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THE NATION'S FOOD

A SURVEY OF SCIENTIFIC DATA

Edited by A. L. BACHARACH, M.A.(Cantab), F.R.I.C. and THEODORE RENDLE, F.R.I.C.

With an Introduction by SIR JOSEPH BARCROFT, C.B.E., F.R.S.

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Some thirty authors have contributed to this book. Many of them are well known for their original contributions in the fields of biochemistry or food technology. They come from laboratories at academic centres, at government research institutions and at food factories. The book thus represents a piece of scientific collaboration by experts selected without any consideration other than their ability to assemble information and give it accurate expression. The authors have brought together all the knowledge at present available about the composition of the foods, and therefore the diets, of the British people. This has involved a detailed examination of seven main foods or groups of foods and the recording of innumerable data giving their chemical compositions.

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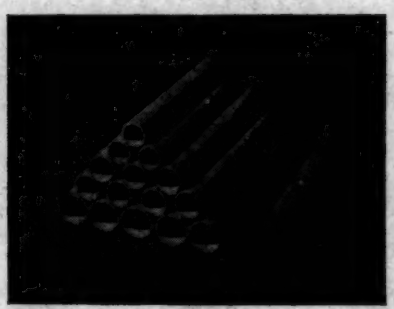

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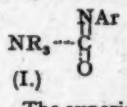
135. *The Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part XIII.* Kinetic Examination of the Reaction of Aryl* iso*Cyanates with Methyl Alcohol.*

By John W. Baker and J. B. Holdsworth.

The velocity of the reaction R·N:C:O + MeOH ⟶ NHR·CO_2Me has been determined in di-*n*-butyl ether solution at 20° for various aryl *iso*cyanates. The reaction is shown to be a base-catalysed addition of the alcohol to the C:O group of the *iso*cyanate (see p. 716, footnote) and, in the presence of a constant concentration of a tertiary base, follows second-order kinetics. In the absence of a base catalyst the " spontaneous " reaction is autocatalysed by the weakly basic urethane product. Unlike the heterocyclic and aliphatic tertiary bases, the dialkylanilines of comparable basic strength have almost no catalytic effect. Calculation of the repulsion energies between non-bonding groups in the formation of the intermediate reaction-complex (I) between the linear ⁻N:C:O group and the bases triethylamine, pyridine, and dimethylaniline, shows that these are much greater in the case of the dialkylaniline molecule, which is flattened by resonance, and are of such a magnitude as to confirm the suggestion that steric effects alone are sufficient to explain the lack of catalytic effect in this class of base.



(I.)

The experimental velocity order R = *p*-NO_2·C_6H_4 ≫ C_6H_5 > *p*-Me·C_6H_4 > *p*-MeO·C_6H_4 ≫ *cyclo*C_6H_{11} is in agreement with the view that the reaction velocity is increased by increased conjugation of the unshared electron pair on the nitrogen in the *iso*cyanate group with the group R.

The well-known reaction between aryl *iso*cyanates and alcohols is usually regarded as occurring thus :

$$Ar\cdot N{:}C{:}O + ROH \longrightarrow Ar\cdot N{:}C(OH)OR \longrightarrow Ar\cdot NH\cdot CO_2R \quad . \quad . \quad . \quad . \quad . \quad (a)$$

and a mechanism of this type was assumed in the addition of the olefin–stannic chloride acid complex to phenyl *iso*cyanate (*J.*, 1945, 724). Lack of suitable methods for the quantitative determination of either reactant or of the product probably accounts for the fact that no detailed kinetic studies of the alcohol–*iso*cyanate reaction seem to have been made. All earlier work has relied either on competition experiments, using two different alcohols in competition for a quantity of *iso*cyanate only sufficient for one of them (Davis and MacFarnum, *J. Amer. Chem. Soc.*, 1934, **56**, 883), or on the determination of yields of isolated urethane obtained under approximately standard experimental conditions after varying periods of reaction time (cf., *inter alia*, Naegali, Tyabji, Conrad, and Litwan, *Helv. Chim. Acta*, 1938, **21**, 1100, 1127; Tarbell, Mallatt, and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 2229).

Preliminary attempts to follow the reaction between methyl alcohol and an aryl *iso*cyanate in a suitable solvent by a thermochemical method were unsatisfactory, but the chemical method for the determination of *iso*cyanate worked out by Strafford and Stagg of Imperial Chemical Industries, Ltd. (Dyestuffs Division) (*Analyst*, 1946, **71**, 557) proved to be very adaptable for the purpose and made possible a detailed study of the *iso*cyanate–alcohol reactions at 20° and in di-*n*-butyl ether as a suitable inert solvent. This paper, which is the first of a series, deals with the interesting conclusions relating to the detailed mechanism of the reaction which have been derived from a study of the reaction between a single alcohol, methyl alcohol, and various aryl *iso*cyanates under different experimental conditions.

When the necessary precautions for the rigid exclusion of moisture were taken, it was shown that (1) the *iso*cyanate does not react with the solvent, di-*n*-butyl ether, and (2) the over-all reaction (*a*) is irreversible under the experimental conditions used and is free from any side reaction, the urethane being the sole product.

Preliminary kinetic investigations on the interaction of phenyl *iso*cyanate with dry methyl alcohol, both approximately 0·25M in di-*n*-butyl ether, at 20°, gave irregular results which were not always reproducible. In general, the values of the first-order coefficient k_1 showed a marked downward drift as the reaction proceeded, whilst those of the second-order coefficient k_2 remained approximately constant, with a tendency to drift upwards in the later stages of the reaction. The observations (cf. Tarbell *et al.*, *loc. cit.*, and references there cited) that urethane formation is base-catalysed suggested that the irregularities might be due to adventitious base-catalysis, and that the upward drift of k_2 might result from weak catalysis of the reaction by the urethane product, functioning as a very weak base. Confirmation of this hypothesis was found in the demonstration of the catalytic effect of added urethane; the

* The communication in *J.*, 1941, 796 was erroneously numbered X instead of XI. Part XI (*J.*, 1942, 191) should be renumbered XII.

results are summarised in Table I. It was shown, that, under the experimental conditions, no permanent compound formation occurs between the aryl *iso*cyanate and the urethane.

TABLE I.

Catalytic effect of added NHPh·CO_2Me *on the reaction between* Ph·NCO *and* MeOH, both 0·24M *in dry di-n-butyl ether at* 20°.

Mol. ratio [NHPh·CO_2Me]/[MeOH]	1	2	2·75	0 (uncatalysed)
Exptl. 10^3k_2 (g.-mol.$^{-1}$ l. min.$^{-1}$)	0·26	0·32	0·36	0·17
Calc. 10^3k_2 (g.-mol.$^{-1}$ l. min.$^{-1}$)	0·24	0·32	0·37	—

When the molecular ratio of the initial concentration of added urethane to the reactants is < 2, the relative change in concentration of the weak catalyst urethane as the reaction proceeds is too small to cause any detectable acceleration, and the experimental data accord well with the kinetics of a second-order reaction. When only one molecular proportion of urethane was added initially, the second-order reaction plot soon deviated from a straight line and gave definite indications of autocatalysis. Under such experimental conditions the reaction should be more accurately represented by the expression $dx/dt = k_0(a - x)^2 + k_b(a - x)^2(a + x)$. This is of the form of $dx/dt = (a - x)^2(K + k_bx)$, where $K = k_0 + k_ba$. Integration of this gives

$$(K + k_ba)t = \frac{x}{a(a - x)} + \frac{k_b}{k_ba + K} \cdot \ln \frac{a(K + k_bx)}{K(a - x)}$$

i.e.,

$$(k_0 + 2k_ba)t = \frac{x}{a(a - x)} + \frac{k_b}{k_0 + 2k_ba} \cdot \ln \frac{a\{k_0 + k_b(a + x)\}}{(a - x)(k_0 + k_ba)}$$

Owing to the difficulty of deriving a straight-line plot from such a complex expression, its validity was tested in an experiment in which $a = 0{\cdot}24$ (k_0 being experimentally evaluated from the "spontaneous" reaction as 0·0017) by solving graphically for k_0 for each of the experimental values of t and x. These values (Table II, col. 4), although approximately constant, still show a small but pronounced upward drift in the later stages of the reaction. The same tendency is revealed when the mean value $k_b = 0{\cdot}0031$ is substituted in the above expression and the values of t are calculated for each of the experimental values of x.

TABLE II.

Autocatalysed reaction of Ph·NCO *and* MeOH, *both* 0·24M *in di-n-butyl ether at* 20°, *in the presence of* 0·24M-*added* NHPh·CO_2Me.

Experimental data.				
t, mins.	x, g.-mol./l.	$a-x$, g.-mol./l.	10^3k_b, g.-mol.$^{-1}$ l. min.$^{-1}$.	t calc. (mins.) for k_b = 0·0031.
180	0·0211	0·2188	0·21	—
410	0·0468	0·1936	0·28	402
1145	0·1002	0·1397	0·30	1140
1440	0·1146	0·1253	0·31	1436
1830	0·1317	0·1082	0·33	1883
2590	0·1547	0·0852	0·36	2746
3200	0·1669	0·0730	0·36	3413
4110	0·1809	0·0590	0·38	4500

A further check on the essential correctness of the value $k_b = 0{\cdot}0031$ is obtained by its application to the data in Table I. The expression $dx/dt = 0{\cdot}0017(a - x)^2 + 0{\cdot}0031(a - x)^2(c + x)$ (where c = concentration of added urethane) may be written as $dx/dt = (a - x)^2\{0{\cdot}0017 + 0{\cdot}0031(c + x)\}$. In the initial stages of this product-catalysed reaction (x very small) this simulates the ordinary second-order reaction expression $dx/dt = (0{\cdot}0017 + 0{\cdot}0031c)(a - x)^2$, and the calculated values of k_2 in Table I are the evaluation of $0{\cdot}0017 + 0{\cdot}0031c$ for the various values of c. The agreement with the experimental values is satisfactory.

Attention was next directed to the elucidation of the mechanism of the base catalysis, a series of tertiary bases of different basic strength being used and in varying concentrations. The powerful catalytic effect of triethylamine, already noticed qualitatively, is confirmed quantitatively by the data given in Table III.

The plot of [NEt_3] against 10^3k_2 gives a straight line, showing that the catalytic effect is directly proportional to the concentration of the basic catalyst. The calculated values of

10^3k_2 in Table III are derived from the more exact expression $k_2 = 0{\cdot}17 \times 10^{-3} + 7{\cdot}45[NEt_3]$, where the value $0{\cdot}17 \times 10^{-3}$ is that for the slow uncatalysed reaction (determined from the

TABLE III.

Reaction between Ph·NCO *and* MeOH, *both* 0·2315M, *in the presence of different concentrations of* NEt_3, *in di-*n*-butyl ether at* 20°.

$[NEt_3]$, M.	0·2158	0·1079	0·0610	0·0306	0·0
Exptl. 10^3k_2	158	80·9	47·5	22·9	0·17
Calc. 10^3k_2	161	80·6	45·6	23·0	—

initial velocity) and 7·45 is the catalytic coefficient (k_c) for triethylamine. Reproducible results giving a good second-order constant over nearly the whole course of the reaction were always obtained in the presence of added tertiary base catalyst, and all future experiments were carried out under these conditions: a base concentration of approximately 0·03M usually gave velocities convenient for measurement.

The simulated bimolecular character of the *iso*cyanate–alcohol reaction in the presence of constant base concentration is confirmed by the results in Table IV, which show the effect of varying the concentration ratio *iso*cyanate/methyl alcohol. The lower value of k_2 in the presence of a large excess of alcohol is significant, and will be discussed more fully in a further publication.

TABLE IV.

Effect of variation of the relative concentrations of Ph·NCO *and* MeOH *on the value of* 10^3k_2 *at* 20°: $[NEt_3] = 0{\cdot}0305$M.

[Ph·NCO], g.-mol./l.	[MeOH], g.-mol./l.	Ratio [MeOH]/[Ph·NCO].	10^3k_2.
0·2315	0·2315	1	22·6
0·2380	0·2380	1	22·8
0·1190	0·2380	2	22·0
0·2380	0·1190	0·5	22·0
0·1241	0·4941	4	19·4

A study of the relationship between the strength of the basic catalyst and its catalytic efficiency revealed a very interesting fact. The results for a series of tertiary bases are given in Table V.

The catalytic effects of the tertiary bases in Set A run parallel with their basic strengths, and a plot of $\log_{10} K_b$ against $\log_{10} k_c$ gives a nearly straight line in accordance with the Brønsted relationship $\log k_c = x \log K_b + G$. The equally strong bases, the dialkylanilines, in Set B, however, exert almost no catalytic action, the values of 10^3k_2 in these experiments being nearly the same as that for the uncatalysed reaction. Discussion of this important anomaly is deferred until later in this paper, after the effect on the reaction velocity of substituents in the phenyl group of the aryl *iso*cyanate has first been considered.

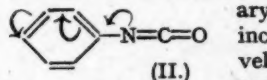
TABLE V.

Catalysis of the Ph·NCO–MeOH *reaction, both* 0·2419M *in di-*n*-butyl ether, by various tertiary bases at* 20°.

Base, and $K_b^{25°}$.	Base concn., g.-mol./l.	10^3k_2.	k_c.	Base, and $K_b^{25°}$.	Base concn., g.-mol./l.	10^3k_2.	k_c.
			Set A.				
Quinoline, $6{\cdot}3 \times 10^{-10}$	0·0306	1·04	0·29	α-Picoline, 3×10^{-8}	0·0306	2·00	0·61
	0·0612	1·98			0·0612	3·99	
Pyridine, $2{\cdot}3 \times 10^{-9}$	0·0306	1·88	0·56	Triethylamine, $5{\cdot}65 \times 10^{-4}$	0·0306	22·9	7·45
	0·0612	3·57			0·0612	47·5	
			Set B.				
Diethylaniline, $4{\cdot}5 \times 10^{-8}$	0·0306	0·175	—	Dimethylaniline, 1×10^{-9}	0·0306	0·20	—
	0·0612	0·19					
(Uncatalysed)	—	0·17	—				

In the later discussion of the mechanism of the reaction it is shown that urethane form-

ation is most probably a base-catalysed addition to the carbonyl group in the *iso*cyanate * and it would therefore be anticipated that the conjugation of the unshared electron pair on the adjacent nitrogen atom, $^{-}\overset{\curvearrowright}{N}=\overset{\curvearrowright}{C}=O$, would retard such addition, since it would provide an internal mechanism for satisfying the unsaturation of the carbonyl group. It would follow, therefore, that increased conjugation of this nitrogen unshared electron pair with an attached aryl group, by providing alternative locations for it as in (II), should increase the carbonyl group unsaturation and hence lead to increased velocities of urethane formation. Qualitatively, this conclusion is supported by the general experience that aryl *iso*cyanates react more readily with alcohols than do alkyl *iso*cyanates, and also by the results of Naegeli *et al.* (*loc. cit.*), but quantitative data have now been obtained by measuring the velocities of reaction of various substituted aryl *iso*cyanates with methyl alcohol under standard conditions of base catalysis. If the velocity of reaction with phenyl *iso*cyanate is taken as a reference standard, introduction of electron-repelling substituents, such as methyl and methoxyl, into the para-position, should decrease the nitrogen conjugation with the aromatic nucleus and hence should decrease the reaction velocity. Conversely, similar introduction of the strongly electron-attracting nitro-group should greatly increase reaction velocity because of the incidence of structures of the type (VI) in the resonance hybrid.



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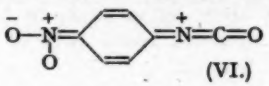


(VI.)

Saturation of the benzene ring by reduction to *cyclo*hexyl, by removing all possibility of conjugation of the nitrogen electrons with the ring, should very greatly reduce the reaction velocity, since the sole conjugation is now with the carbonyl group. Hence, theoretical considerations predict the order

$$R = \textit{cyclo}\text{hexyl} \ll p\text{-MeO}\cdot C_6H_4 < p\text{-Me}\cdot C_6H_4 < Ph \ll p\text{-}NO_2\cdot C_6H_4$$

for the velocities of reaction of R·NCO with methyl alcohol. The results in Table VI completely confirm this conclusion.

TABLE VI.

Reaction between R·NCO *and* MeOH, *both* 0·24M *in di*-n-*butyl ether, at* 20° *in the presence of* (a) 0·0306M- *and* (b) 0·0612M-*triethylamine.*

R = *cyclo*Hexyl.		*p*-MeO·C_6H_4.	*p*-Me·C_6H_4.	C_6H_5.	*p*-NO_2·C_6H_4.
10^3k_2	(a) 0·021	9·9	12·3	22·6	~3000
	(b) 0·04$_3$	18·8	24·0	47·5	—

The reaction with *p*-nitrophenyl *iso*cyanate is much too fast for accurate measurement; the figure given is based on one reading when 0·0305M-triethylamine was used (reaction >90% complete in 4 minutes), confirmed by extrapolation from an experiment in which only 0·0005M-catalyst was used ($10^3k_2 = 56·9$, whence for 0·0305M-catalyst, $10^3k_2 = 3482$).

Discussion of Results.

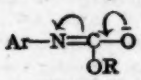
The slow " spontaneous " reaction of an aryl *iso*cyanate with methyl alcohol in di-*n*-butyl ether is found to be catalysed by the addition of tertiary bases, and the rate of reaction is then found to follow the equation

$$\frac{d[Ar\cdot NCO]}{dt} = \frac{d[MeOH]}{dt} = k_0[Ar\cdot NCO][MeOH] + k_c[Ar\cdot CO][MeOH][Base]$$

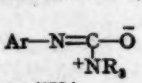
Hence the bimolecular reaction coefficient is

$$k_{bi} = \frac{1}{[Ar\cdot NCO][MeOH]} \cdot \frac{d[Ar\cdot NCO]}{dt} = k_0 + k_c[Base] \quad . \quad . \quad . \quad . \quad (i)$$

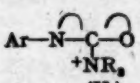
* This statement is not meant to imply that the unsaturation of the $^{-}N{:}C$ group in the *iso*cyanate is ignored. From the kinetic standpoint we regard the reaction as complete when the ion (III) of the product has been formed, the subsequent co-ordination of the proton being regarded, in accordance with generally accepted views, as instantaneous. In this ion, as in that of the intermediate base



(III.)



(IV.)



(V.)

complex (IV), the true structure is, doubtless, a resonance hybrid of the general type (V). The essential feature is that the mechanism of addition of an alcohol to an *iso*cyanate is regarded as of the same type as other base-catalysed additions to carbonyl compounds, such as aldol, cyanohydrin, etc., reactions.

These reaction kinetics are consistent with the following mechanism of reaction :

$$\text{Ar·NCO} + \text{Base} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Complex}$$

$$\text{Complex} + \text{MeOH} \xrightarrow{k_3} \text{NHAr·CO}_2\text{Me} + \text{Base}$$

$$\text{Ar·NCO} + \text{MeOH} \xrightarrow{k_0} \text{NHAr·CO}_2\text{Me}$$

Using the stationary state condition, the concentration of the complex is given by the expression

$$\text{Complex} = \frac{k_1[\text{Ar·NCO}][\text{Base}]}{k_2 + k_3[\text{MeOH}]}$$

and hence the rate of formation of the product, urethane, may be expressed as

$$\frac{d[\text{Ar·NCO}]}{dt} = k_0[\text{MeOH}][\text{Ar·NCO}] + \frac{k_1k_3[\text{Ar·NCO}][\text{MeOH}][\text{Base}]}{k_2 + k_3[\text{MeOH}]}$$

or

$$k_{bi} = k_0 + \frac{k_1k_3[\text{Base}]}{k_2 + k_3[\text{MeOH}]} \quad \ldots\ldots\ldots\ldots \quad \text{(ii)}$$

If the value of k_2 is always very much greater than k_3[MeOH] under the conditions of experiment, then equation (ii) reduces to

$$k_{bi} = k_0 + \frac{k_1k_3}{k_2}[\text{Base}] = k_0 + Kk_3[\text{Base}] \quad \ldots\ldots\ldots \quad \text{(iii)}$$

in which $K = k_1/k_2$ is the equilibrium constant of the complex formation. Equation (iii) is identical with the experimental equation (i) if we identify $k_c = Kk_3$.

The equilibrium constant k_1/k_2. The experimental results, although pointing to the formation of a complex between the base catalyst and the *iso*cyanate,* give no information as to the nature of the complex. On generally accepted views regarding the mechanism of base-catalysed additions to the carbonyl group it seems to us that a probable structure of the complex would be $\text{Ar—N=}\underset{\overset{|}{{}^+\text{NR}_3}}{\text{C}}\text{—O}^-$ (cf. footnote, p. 716). If this is the case it is interesting to compare the following reactions :

$$\text{(I)}\ \text{NR}_3 + \text{CR}_3\text{—X} \rightleftharpoons \text{R}_3\overset{+}{\text{N}}\text{—CR}_3 + \overset{-}{\text{X}}$$

$$\text{(II)}\ \text{NR}_3 + \text{H·OH} \rightleftharpoons \text{R}_3\overset{+}{\text{N}}\text{H} + \overset{-}{\text{O}}\text{H}$$

$$\text{(III)}\ \text{NR}_3 + \text{Ar}\underset{\text{C=O}}{\text{N}} \rightleftharpoons \text{R}_3\overset{+}{\text{N}}\text{—}\underset{\text{O}^-}{\overset{\text{NAr}}{\text{C}}}$$

The energy changes involved in these reactions will be, respectively,

$$\text{(I)} + D_{\text{C–N}^+} - I'_{\text{N}} + E_{\text{X}} - D_{\text{C–X}} + S_{\text{X}'} + S_{\text{N}^+}$$

$$\text{(II)} + D_{\text{H–N}^+} - I''_{\text{N}} + E_{\text{OH}} - D_{\text{H–OH}} + S_{\text{OH}'} + S_{\text{N}^+}$$

$$\text{(III)} + D_{\text{C–N}^+} - I'''_{\text{N}} + E_0 - D_{\text{C=O}} + S$$

where $D_{\text{C–N}^+}$ is the strength of the N–C bond in the quaternary ammonium compound, I_{N} is the ionisation potential of the nitrogen in the base, E is the electron affinity of the centre which forms the negative ion, $D_{\text{C–X}}$, $D_{\text{H–OH}}$, and $D_{\text{C=O}}$ are the strengths of the bond broken in each reaction, and S is the energy of solvation.

With the same reactant and with varying bases one would expect, in the first place, that the variations of the heats of reaction would depend mainly on variations in I_{N} and, to a lesser extent, on the solvation energy of the quaternary ammonium compound. If this were true, therefore, a parallel variation in the heats of formation and the equilibrium constants of the Menschutkin reaction, the base formation, and the complex formation might be expected. Unfortunately, the only data available for this comparison are those for the basic dissociation constants and the catalytic coefficient k_3k_1/k_2 for the reaction under discussion. The data in Table V, however, reveal two striking anomalies in this comparison. Whereas there is a parallelism in the trends of log k_3k_1/k_2 (k_c) and log K_b for the Set A bases, quinoline, pyridine,

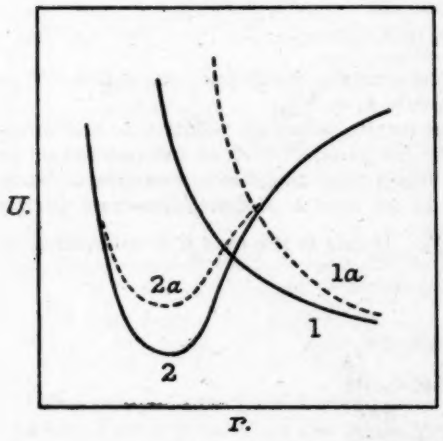
* The other possible mode of action of the base catalyst would be to increase the ionisation of the hydrogen from the alcohol by an equilibrium of the type $\text{ROH} + \text{B} \rightleftharpoons \text{RO}^- + \text{BH}^+$. If this were the case there seems to be no valid explanation why the dialkylanilines should not show a normal catalytic activity in accordance with their basic strength, and their anomalous behaviour renders such a mechanism very improbable.

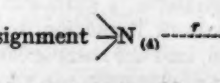
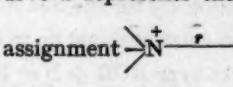
α-picoline, and triethylamine, yet the catalytic effects of the Set B bases, the dialkylanilines, are very much smaller than would be expected from their basic dissociation constants.

There are two possible causes of this anomalous behaviour. One is that in the case of the dialkylanilines the formation of the complex might be accompanied by a large negative entropy change. In this connection it is important to remember that the abnormal slowness of the Menschutkin reaction (I, p. 717) is due to the large negative entropy change accompanying the formation of the transition-state complex. In the present case, however, there is little difference in the moments of inertia between molecules such as quinoline and α-picoline, which show normal behaviour, and the dialkylanilines, which are abnormal, and it is not possible that such small changes in moments of inertia should cause large variations in the entropy change accompanying association.

In the above discussion the argument for a parallel behaviour between bases and complex formation rested on the assumption that the value of D_{O-N^+} remained sensibly constant from one base to another. There is now evidence that, with heavily substituted centres, the energy of bond formation may be profoundly modified by the energy of repulsion between the substituent groups which are not directly involved in the bond. For example, Polanyi and Evans have shown (*Nature*, **1943**, **152**, 738) that the heat of polymerisation of *iso*butene is reduced by 10 k.-cals. per mole by the repulsion energy between the substituent methyl groups, and recently Dostrovsky, Hughes, and Ingold (*J.*, **1946**, 173) have calculated that the activation energy of bimolecular bromine exchange in the *neo*pentyl halides is increased by a value of 11·7 k.-cals. per mole by steric repulsion. At the time when we had formed the opinion that steric factors might explain the anomalous catalytic behaviour of the dialkylanilines in the *iso*cyanate–alcohol reaction, Dostrovsky, Hughes, and Ingold had just completed their quantitative assessment of this factor in certain cases of the bimolecular halogen replacement reaction in alkyl halides. We are greatly indebted to Professor Ingold for allowing us to see the manuscript of their (then unpublished) paper and for the suggestion that it might be worth while to attempt a similar quantitative treatment of steric effects in the formation of the base–*iso*cyanate complex. We also wish to express our deep appreciation to Professor M. G. Evans, of the Department of Physical and Inorganic Chemistry, for much invaluable advice and continual assistance in the development of such a treatment.

FIG. 1.



In the case of the *iso*cyanate–base complex steric effects between the substituent groups may have one of two effects: (*a*) the repulsion energy may have the effect of increasing the activation energy of complex formation, and so reducing the magnitude of k_1 to such a value that the reaction scheme set out on p. 717 is no longer applicable and stationary state conditions for the concentration of the complex cannot be applied; * (*b*) the repulsion energy between the substituent groups in the final complex may be so large as to reduce the heat of formation of the complex and hence the value of k_1/k_2. These two possibilities are shown diagrammatically in Fig. 1. Curve 1 represents the change in potential energy as a function of the distance r for the bond assignment  and in the absence of repulsion energy between the substituent groups on centre $N_{(4)}$ and $C_{(1)}$. Curve 1*a* represents the same system when the size and configuration of substituent groups are such that there is a large repulsion energy between them. Curve 2 represents the change in potential energy as a function of the distance r for the bond assignment  in the absence of repulsion energy between

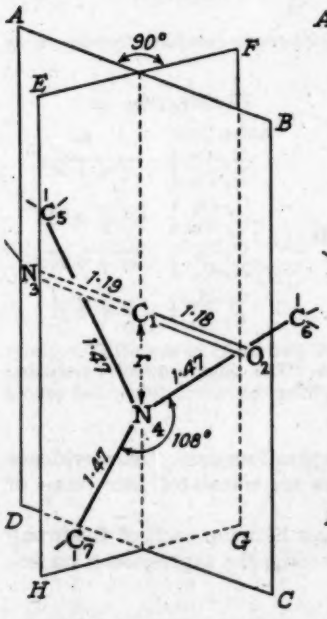
* Preliminary experimental evidence suggests that, in the *absence* of base catalysis, the alcohol–*iso*cyanate reaction may, in fact, proceed by a different mechanism.

substituent groups, and curve 2*a* the same system where repulsion energy comes into play. It is important to note that, for the corresponding values of r, the value of the repulsion energy will not be the same for curve 2 and curve 1 because of the change in the bond character of the substituent groups. These will have a different configuration in the two cases.

The influence of repulsion energy on curve 1. In the case under consideration information as to configurations, polarisabilities, and ionisation potentials of the centres involved is much less certain than it is in the case dealt with by Dostrovsky, Hughes, and Ingold (*loc. cit.*) or in other cases previously examined, and hence any discussion of the repulsion energy must be considered as only semi-quantitative.

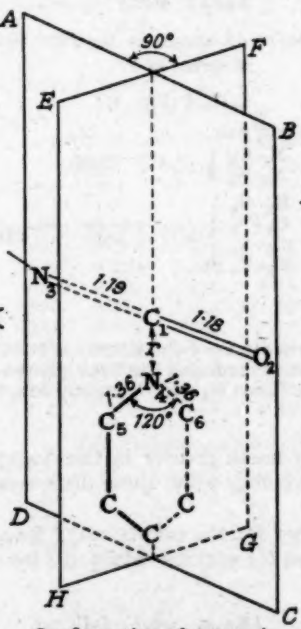
Such treatment has been attempted in three typical cases, *viz.*, for triethylamine, pyridine, and dimethylaniline. The structure of the $-N{:}C{:}O$ group of the aryl *iso*cyanate has been taken as a linear configuration with the distances $r_{NO} = 1{\cdot}19$ A. and $r_{CO} = 1{\cdot}18$ A. given by Cowley and Partington (*J.*, 1935, 46), based on dipole moment measurements. The dialkylaniline molecule has been assumed to be flat with the alkyl groups in the plane of the benzene

FIG. 2.



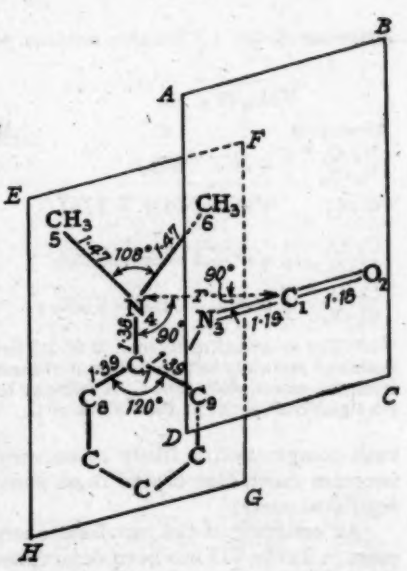
Configuration of groups in $N(CH_3)_3$–Ar·NCO *approach.*

FIG. 3.



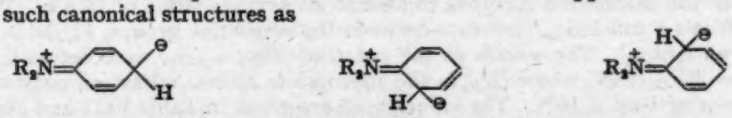
Configuration of groups in C_5H_5N–Ar·NCO *approach.*

FIG. 4.



Configuration of groups in $NPhMe_2$–Ar·NCO *approach.*

ring. The basis of this assumption is that this molecule has an appreciable resonance energy arising from such canonical structures as



which will tend to flatten the whole structure. The normal structures and bond distances have been taken for triethylamine and pyridine.

In each of the three cases the most favourable orientation of approach of the base catalyst to the *iso*cyanate group has been chosen, *viz.*, that in which there is minimum interference between the various pairs of atoms or groups involved so that compression would be a minimum. Such orientations are represented in Figs. 2, 3, and 4 for triethylamine, pyridine, and dimethylaniline, respectively. In Fig. 2 the linear group $N{:}C{:}O$ is in the plane *ABCD* and the atoms C_1–N_4–C_7 (Me) are in the plane *EFGH* at 90° with *ABCD*, the atoms C_1–N_4 being in the line of intersection of the planes at a distance r A. apart. The various bond lengths and angles used are the experimentally determined values recorded in the literature. In Fig. 3 the group $N{:}C{:}O$ is in the plane *ABCD* and the plane of the pyridine ring is in the plane *EFGH* at right

angles, atoms C_1–N_4 again being in the line of intersection of the planes at a distance r A. apart. Examination of scale models showed that the optimum method of approach of the dimethylaniline molecule to the *iso*cyanate is that depicted in Fig. 4. The N:C:O group is in the plane *ABCD* parallel to the plane, *EFGH*, of the planar dimethylaniline molecule. The angle C_7–N_3–C_1 is 90°, C_1 being vertically over N_4.

From the geometry of these orientations the values of the distances d between the various pairs of atoms or groups have been calculated in terms of r, the distance between the base nitrogen atom N_4 and the carbon atom C_1 of the *iso*cyanate group. The values of d (in A.), for all pairs which might show significant compression, are recorded in Table VII. For simplicity the case of NMe_3 has been used instead of NEt_3 in Fig. 1, since the β-carbon atoms of the ethyl groups are too far away to exert any appreciable effects.

Casual inspection of Table VII immediately reveals that, apart from the distances N_4–O_2 and N_4–N_3, which are common to all three cases, the most important compression is likely to occur between the methyl groups C_5 and C_6 and the atoms N_3 and O_2, respectively, and that

TABLE VII.

Distances d (*in* A.) *between various pairs of atoms in the base–isocyanate complex formation in in terms of* r.

NMe_3 (Fig. 2).		C_5H_5N (Fig. 3).		$NPhMe_2$ (Fig. 4).	
Atom pair.	d.	Atom pair.	d.	Atom pair.	d.
N_4–O_2 *	$\sqrt{r^2 + 1{\cdot}393}$	N_4–O_2	$\sqrt{r^2 + 1{\cdot}393}$	N_4–O_2	$\sqrt{r^2 + 1{\cdot}393}$
N_4–N_3		N_4–N_3		N_4–N_3	
C_1–C_7	$\sqrt{r^2 + 1{\cdot}051r + 2{\cdot}161}$	C_5–O_2	$\sqrt{r^2 + 1{\cdot}36r + 3{\cdot}248}$	C_6–O_2	$\sqrt{r^2 + 0{\cdot}706}$
C_6–O_2	$\sqrt{r^2 + 1{\cdot}045r + 0{\cdot}746}$	C_6–O_2		C_5–N_3	
C_5–N_3		C_5–N_3		O_2–C_9	$\sqrt{r^2 + 4{\cdot}312}$
C_7–O_2	$\sqrt{r^2 + 1{\cdot}045r + 3{\cdot}554}$	C_6–N_3		N_3–C_8	
C_7–N_3				C_7–O_2	$\sqrt{r^2 + 3{\cdot}31}$
				C_7–N_3	

* The recorded difference (0·01 A.) between the bond distances N=C and C=O in the –N:C:O group is almost certainly within the error of measurement and has been ignored. The extra symmetry resulting from the assumption that C_1 is midway between N_3 and O_2 greatly simplifies the calculations, and causes no significant error in the values of d.

such compression is likely to be very much greater in the dialkylaniline case. The evidence becomes much clearer and more convincing when these distances are translated into terms of repulsion energy.

An estimate of the repulsion energy for the non-bonding forces between each of the group pairs in Table VII has been determined for various values of d by using the expression (London, *Z. physikal. Chem.*, 1930, *B*, **11**, 222).

$$U = -\left\{\frac{3}{2}\frac{\alpha_1\alpha_2}{d^6} + \frac{b}{d^3}\right\}\frac{I_1I_2}{I_1 + I_2}$$

For the ionisation potential I_1 and I_2 it was considered sufficiently accurate for the approximate nature of the calculation involved to assume an average value of 12 e.v. When $d = d_0$, the van der Waals " touching " distance between the respective groups, $\delta U/\delta d = 0$, whence b is calculated as $d_0^3\alpha_1\alpha_2$. The values of the polarisabilities α_1, α_2, were determined from the expression $\alpha = 3[R_D]/4\pi N$, where $[R_D]$ is the appropriate atomic refraction constant, and N is Avogadro's number $6{\cdot}02 \times 10^{23}$. The values used are given in Table VIII and are taken from Landolt–Börnstein " Tabellen " except where otherwise stated.

By plotting the values of U so obtained against d for each of the interacting pairs of atoms or groups in Table VII the various compression energies for any value of d (and hence, from the data on Table VII, for any value of r) could be evaluated. Summation of these energies for all the interacting groups then gave ΣU, the total energy increment due to compression for any required value of r. This ΣU represents a *maximum* value for the energy due to compression, to be added to the corresponding repulsion energies for the approach of N_4 to C_1 (similarly calculated by means of the equation above). Thus data for the plotting of both Curve 1 and Curve 1*a* in Fig. 1 were obtained. The actual energy increments for values of r between 1·0 and 2·6 A. are given in Tables IX for the catalysts triethylamine, pyridine, and dimethylaniline.

TABLE VIII.

NEt_3 case (as NMe_3).

Atom.		$[R_D]$, c.c.	$10^{24}\alpha$.	
N_4	N in NR_3,	2·92	1·15	
N_3	N in C—N—C,	4·10	1·62	
O_2	O in C=O,	2·287	0·92	
CH_3		—	2·2	(Evans and Warhust, *Trans. Faraday Soc.*, 1939, **35**, 596.)
C_1	{ C, 2·41 + double bond, 1·7 }	4·11	1·62	

C_5H_5N case.

N_4	N in C—N—C, 4·10	1·62	
C_5, C_6	C + H = 2·41 + 1·09 = 3·5	1·38	

$NPhMe_2$ case.

N_4	N in $NArR_2$, 4·363	1·72	

van der Waals radii: CH_3, 2·0; C, 1·6; N, 1·5; O, 1·4; $CH = C + \frac{1}{2}\{2·0 - 1·6\} = 1·73$ A. (Pauling " The Nature of the Chemical Bond," 1945, p. 189).

TABLE IX.

Correlation of various non-bonding distances (d) *with* r *and corresponding values of* U (*in electron volts*).

(*a*) Triethylamine as catalyst.

	N_4–N_3.		N_4–O_2.	C_1–C_7.		O_2–C_6.		N_3–C_6.	O_2–C_7.		N_3–C_7.	
r, A.	*U.*	*d.*	*U.*	*d.*	*U.*	*U.*	*d.*	*U.*	*U.*	*d.*	*U.*	ΣU.
1	4·634	*1·55*	2·314	*2·05*	0·834	3·888	*1·67*	7·602	0·097	*2·37*	0·216	19·585
1·2	2·010	*1·68*	0·858	*2·21*	0·312	1·380	*1·86*	2·736	0·050	*2·50*	0·109	7·455
1·4	0·864	*1·83*	0·438	*2·36*	0·156	0·840	*2·04*	1·260	0·022	*2·64*	0·053	3·633
1·6	0·360	*1·99*	0·204	*2·53*	0·063	0·210	*2·23*	0·420	0·006	*2·79*	0·019	1·282
1·8	0·138	*2·15*	0·060	*2·70*	0·032	0·074	*2·42*	0·162	—	*2·95*	0·006	0·472
2·0	0·048	*2·32*	0·018	*2·87*	0·011	0·025	*2·61*	0·058	—	*3·11*	—	0·160
2·1	0·026	*2·41*	0·009	*2·96*	0·006	0·015	*2·71*	0·040	—	*3·19*	—	0·094
2·2	0·008	*2·50*	0·002	*3·05*	0·002	0·006	*2·81*	0·018	—	*3·27*	—	0·036
2·4	—	*2·68*	—	*3·32*	—	—	*3·00*	—	—	*3·44*	—	—
2·6	—	*2·86*	—	*3·42*	—	—	*3·20*	—	—	*3·61*	—	—

(*b*) Pyridine as catalyst.

	N_3–N_4.		O_2–N_4.	*d.*	O_2–C_5.	O_2–C_6.	N_3–C_5.	N_3–C_6.	
r, A.	*U.*	*d.*	*U.*		*U.*	*U.*	*U.*	*U.*	ΣU.
1	6·534	*1·55*	3·257	*2·37*	0·035	0·035	0·078	0·078	10·017
1·2	2·808	*1·68*	1·398	*1·51*	0·013	0·013	0·033	0·033	4·298
1·4	1·218	*1·83*	0·594	*2·67*	0·003	0·003	0·012	0·012	1·842
1·6	0·510	*1·99*	0·252	*2·83*	—	—	—	—	0·762
1·8	0·186	*2·15*	0·072	*2·99*	—	—	—	—	0·258
2·0	0·072	*2·32*	0·030	*3·16*	—	—	—	—	0·102
2·1	0·036	*2·41*	0·012	*3·24*	—	—	—	—	0·048
2·2	0·012	*2·50*	0·002	*3·33*	—	—	—	—	0·014
2·4	—	*2·68*	—	*3·50*	—	—	—	—	—
2·6	—	*2·86*	—	*3·68*	—	—	—	—	—

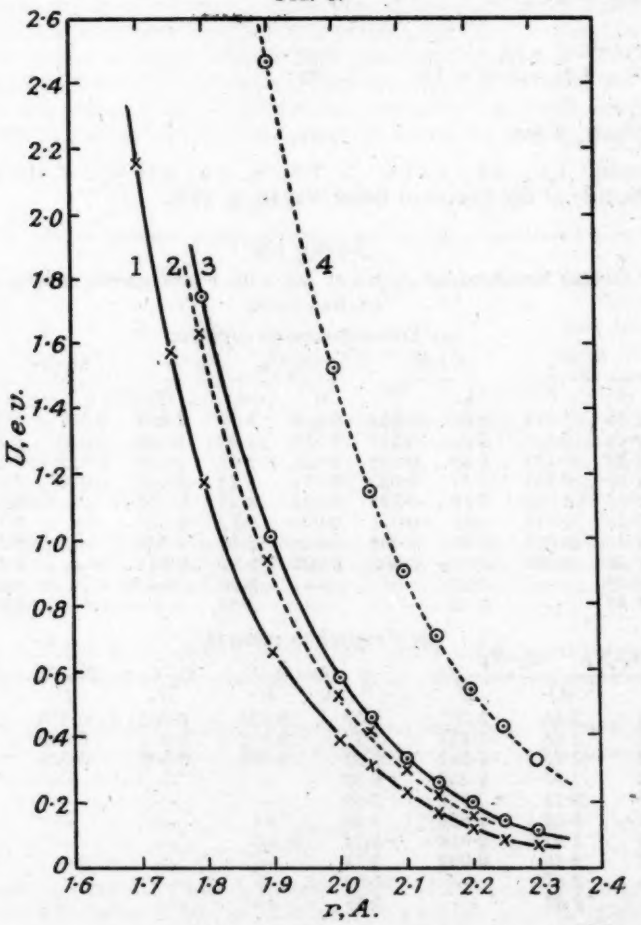
(*c*) Dimethylaniline as catalyst.

	N_3–N_4.		O_2–N_4.	C_6–O_2.		C_6–N_3.	O_2–C_5.		N_3–C_5.	O_2–C_7.		N_3–C_7.	
r, A.	*U.*	*d.*	*U.*	*U.*	*d.*	*U.*	*U.*	*d.*	*U.*	*U.*	*d.*	*U.*	ΣU.
1	6·930	*1·55*	3·463	39·000	*1·31*	75·600	0·051	*2·30*	0·102	0·096	*2·08*	0·207	122·449
1·2	2·988	*1·68*	1·500	14·340	*1·47*	26·700	0·029	*2·40*	0·063	0·055	*2·18*	0·120	45·795
1·4	1·302	*1·83*	0·624	5·100	*1·63*	9·600	0·014	*2·51*	0·035	0·024	*2·29*	0·057	16·756
1·6	0·528	*1·99*	0·264	1·800	*1·81*	3·450	0·006	*2·62*	0·014	0·012	*2·42*	0·024	6·098
1·8	0·192	*2·15*	0·072	0·702	*1·99*	1·380	—	*2·75*	—	0·006	*2·56*	0·012	2·364
2·0	0·072	*2·32*	0·030	0·285	*2·17*	0·540	—	*2·88*	—	—	*2·70*	—	0·957
2·1	0·036	*2·41*	0·012	0·174	*2·26*	0·348	—	*2·95*	—	—	*2·78*	—	0·570
2·2	0·012	*2·50*	0·002	0·128	*2·36*	0·225	—	*3·03*	—	—	*2·85*	—	0·367
2·4	—	*2·68*	—	0·037	*2·54*	0·090	—	*3·17*	—	—	*3·01*	—	0·127
2·6	—	*2·86*	—	0·012	*2·73*	0·030	—	*3·33*	—	—	*3·17*	—	0·042

It is shown later that a probable value of r in the transition complex is ~1·8 A. Inspection of the ΣU values for $r = 1·8$ A. in Table IX, (*a*) and (*b*), shows that the energy increase arising from compression is greater with triethylamine (0·472 e.v.) than with pyridine (0·258 e.v.).

Notwithstanding this adverse factor, the catalytic coefficient of triethylamine (7·45) is much greater than is that (0·56) for pyridine. This must mean that the greater catalytic efficiency of triethylamine is due to its greater basic strength and, in the case of these two catalysts, compression factors probably play only a very minor rôle, so that the pyridine case need not be further considered. With dimethylaniline, however [Table IX (*c*)], the corresponding value of ΣU (2·364 e.v.) is very much greater. The data so far obtained permit the plotting of the repulsion energy curves (1 and 1*a* in Fig. 1) for the cases of triethylamine and dimethylaniline

FIG. 5.



Repulsion energy in the formation of the complex NR_3------C(=O)

1. NEt_3 *without replusion energy.* 3. $NPhMe_2$ *without repulsion energy.*
2. „ *with* „ „ 4. „ *with* „ „

when energy due to compression is taken into account. The relevant data are given in Table X, and the corresponding curves are depicted in Fig. 5.

The differentiation between the values of k_1 for triethylamine and dimethylaniline clearly depends upon the value of r at which the transition state is formed in the two cases. This value cannot be determined without calculating Curve 2 in Fig. 1, which it is not possible to do with the data at present available. The range of values of r in which the transition state value r_T will lie can, however, be defined. This range will extend from $r = 1{\cdot}28$ A. to $r = 2{\cdot}3$ A. The first value is the sum of the covalent radii of carbon (0·77 A.) and N^+ (0·51 A.),*

* This radius of N^+ was obtained by reducing the value for N (0·70 A.) by an amount 0·19 A., which is the contraction in atomic radius for the loss of one electron.

TABLE X.

Repulsion energy $U = a_1a_2\left\{-\frac{1\cdot5}{r^6}+\frac{r_e^3}{r^9}\right\}\frac{I_1I_2}{I_1+I_2}$ . . . e.v. for C_1–N_4.

	NEt_3 as catalyst.			$NPhMe_2$ as catalyst.		
r, A.	U (without compression).	ΣU (from Table IX, *a*).	Total U.	U (without compression).	ΣU (from Table IX, *c*).	Total U.
1·8	1·185	0·472	1·657	1·773	2·364	4·137
1·9	0·675	0·272	0·947	1·010	1·46	2·470
2·0	0·39	0·160	0·550	0·581	0·957	1·538
2·05	0·30	0·120	0·420	0·441	0·715	1·156
2·10	0·224	0·094	0·318	0·335	0·570	0·905
2·15	0·170	0·056	0·226	0·254	0·453	0·707
2·20	0·128	0·036	0·164	0·191	0·367	0·558
2·25	0·099	—	—	0·148	0·288	0·436
2·30	0·072	—	—	0·107	0·220	0·327

and the second is the value of r at which the activation energy would reach a value of 2 k.-cals. and which is certainly a lower limit. Within this range of r the potential-energy curve 1*a*, for dimethylaniline, lies very much higher than that for triethylamine, and hence the value of k_1 for the former catalyst will be considerably smaller than for the latter; *e.g.*, at the mean value $r_T = 1\cdot8$ A., the maximum difference in the compression energy in the formation of the bond $NR_3\ldots C(=NPh)(=O)$ when NR_3 is dimethylaniline and triethylamine, respectively, is 2·364 — 0·472 = 1·892 e.v. = 44 k.-cals. per mol.

Influence of repulsion energy on the equilibrium constant k_1/k_2. The other possibility to be envisaged is that the mechanism set out on p. 717 holds even when the catalytic constant k_3k_1/k_2 is exceedingly small. In this case the anomalous behaviour of the dialkylanilines must be sought in the value of k_1/k_2 and not of k_1 alone. This necessitates an evaluation of the repulsion energy terms in the final state of the complex structure $R_3\overset{+}{N}-C(=NAr)(=O)$. This structure will probably have a different configuration from that of the transition complex because of the change in bond character. Although it has not been possible to carry out detailed calculations in this case, it can be assumed that the large substituent groups on the N^+ and the carbon will have a similar effect to that described in the discussion of the value of k_1, and it is felt that the semi-quantitative treatment which has been possible with the available data do support the view that the very small catalytic effect of the dialkylanilines in the alcohol–*iso*cyanate reaction could be accounted for entirely by steric factors. It should be noted that repulsion terms will not be important in the basic dissociation constants which show no abnormality since, in this case, the hydrogen atom, because of its small size, will not exert any appreciable steric influence.

Further investigations regarding the mechanism of the interaction of the alcohol with the transition complex and of the uncatalysed reaction are in progress.

EXPERIMENTAL.

Materials.—Specimens of liquid *iso*cyanates were either purchased or prepared by the usual method (base hydrochloride and carbonyl chloride in dioxan solution) and were purified by repeated fractional distillation, over phorphoric oxide in the later stages. All specimens were redistilled over phosphoric oxide under reduced pressure immediately before use. The specimens used had the following b. ps.: phenyl 54·0°/16 mm., *p*-tolyl 79·5°/20 mm., *p*-methoxyphenyl 105·9°/16·5 mm., *cyclo*hexyl 59·0°/16·5 mm. The purchased specimen of *p*-nitrophenyl *iso*cyanate was very impure. It was extracted in an all-glass Soxhlet extractor with boiling sodium-dried ligroin (b. p. 40—60°) with rigid exclusion of moisture, until the ligroin solution just began to develop a slight yellow tinge. The ligroin solution was then immediately concentrated to about 200 c.c., filtered hot, and the colourless filtrate allowed to crystallise in a desiccator over phosphoric oxide. The clean, colourless needles were washed by decantation with dry ligroin, dried in a vacuum over phosphoric oxide, and stored in a weighing bottle over phosphoric oxide for use. The product had m. p. 58°.

Methyl phenylcarbamate, prepared by the action of an excess of pure methyl alcohol on pure dry phenyl*iso*cyanate, was purified by repeated crystallisation from ligroin (b. p. 40—60°) and dried over phosphoric oxide in a vacuum; m. p. 48°.

Absolute methyl alcohol (500 c.c.) was refluxed for 10 hours with magnesium turnings (2·5 g.) and mercuric chloride (0·5 g.) and fractionated through a Widmer column; b. p. 64·7°/766 mm.

Tertiary bases, used as catalysts, were usually specimens specially purified for previous kinetic work, dried over potassium hydroxide, and refractioned: triethylamine b. p. 89°, pyridine b. p. 116°, α-picoline b. p. 42·2—42·3°/28 mm., quinoline b. p. 114°/19 mm., diethylaniline b. p. 96·2—96·4°/15·5 mm., piperidine b. p. 35—36°/40 mm. In order to ensure complete absence of primary and secondary bases, dimethylaniline (80 g., "AnalaR") was refluxed with 0·8 g. of "AnalaR" acetic acid for 8 hours and steam-distilled, and the oily layer in the distillate was separated, dried first over anhydrous potassium carbonate and then over potassium hydroxide, and repeatedly fractionated; b. p. 85·5°/20 mm. The base gave a picrate, m. p. 164°, without further purification.

Di-*n*-butyl ether was freed from peroxides by Williamson's method [cf. *Ind. Eng. Chem.* (News Edition), 1939, **17**, 209]. It was then washed (four times) with concentrated hydrochloric acid to ensure freedom from basic compounds, then with water (5 times), and dried, first over calcium chloride and then over sodium. The product was refluxed, under reduced pressure, over clean sodium, fractionated through a Widmer column, and the processes repeated until no action occurred with fresh sodium. The fraction, b. p. 47·4—47·5°/24 mm., was stored in dark bottles for use.

Determination of the Aryl iso*Cyanate*.—The following modification of the method of Strafford and Stagg (*loc. cit.*) was employed.

Solutions used. Hydrochloric acid in constant-boiling alcohol, 0·526(2)N; aqueous sodium hydroxide, 0·525(7)N; indicator, 5 parts of a 0·2% solution of methyl red + 1 part of a 0·5% solution of methylene-blue; piperidine solution, 10 ml. of pure dry piperidine dissolved in pure dry acetone and the solution made up to 100 ml.—this gives an almost exactly molar solution. This solution was stored in the apparatus used by Baker and Hemming (*J.*, 1942, 197; Fig. 2) for sampling the cyanohydrin reaction mixture, the 5-ml. portions of the solution being forced into the ground-in 5-c.c. pipette by slight pressure of dry nitrogen. All other solutions were introduced into the pipettes by slight suction from a filter-pump through flexible rubber leads protected from back diffusion of water vapour by phosphoric oxide drying tubes.

Determination of the calibration curve for phenyl iso*cyanate*. Dry di-*n*-butyl ether (10 ml.) was pipetted into each of six 100-ml. glass-stoppered conical flasks, the flasks cooled in ice, and 5 ml. of the piperidine solution added to each, and washed down into the reaction medium by a few ml. of dry acetone. Various quantities of pure phenyl *iso*cyanate, freshly distilled over phosphoric oxide directly into a weight pipette, were then weighed directly into each of the flasks in turn, which were then left stoppered in ice for 15 minutes. Constant-boiling alcohol (15 ml.) was then added from a burette, followed by 10 ml. of the standard hydrochloric acid and four drops of the indicator, and the mixture was titrated to a *bright* green (sharp end-point) with the standard sodium hydroxide solution. A blank determination was carried out in an identical manner but with omission of the *iso*cyanate. A typical result is as follows:

Blank = 0·380, 0·370, 0·370 ml.; mean = 0·370 ml. of NaOH.

Wt. of Ph·NCO, g.	0·0404	0·0695	0·1147	0·1569	0·1936	0·2324
Vol. of NaOH required, ml.	1·000	1·485	2·200	2·875	3·430	4·055
Less blank, ml.	0·630	1·115	1·830	2·505	3·060	3·685

A plot of weight of Ph·NCO added against the corrected volume of alkali solution required gave a good straight line which was used as a calibration curve for the determination of the weight of phenyl *iso*cyanate present in reaction samples. The weight of phenyl *iso*cyanate calculated from this curve corresponded to 99·1% of the actual weight added in the calibration. A fresh blank was determined for each new batch of piperidine solution (which was discarded as soon as it acquired a faint yellow tinge) and calibration curves for each of the *iso*cyanates used were constructed in a similar manner. It was shown that the addition of the product urethane had no effect on the blank titration.

Preliminary investigations. These were undertaken to prove (*a*) that the *iso*cyanate does not react under the conditions of experiment with (1) the solvent, di-*n*-butyl ether, or (2) the product, methyl phenylcarbamate, and (*b*) that the reaction is essentially irreversible under the conditions of experiment.

(*a*, 1) Pure dry phenyl *iso*cyanate (1·7207 g.) was weighed from a weight pipette into di-*n*-butyl ether, and the solution made up to 50 ml. at 20° in the thermostat. At intervals, 10-ml. samples were taken and the concentration of the solution was determined by the method described above.

Time, mins.	0	570	1390
Ph·NCO, g.-mol./l.	0·2888	0·2888	0·2861

(*a*, 2) Similar experiments were carried out with 50 ml. of a solution containing phenyl *iso*cyanate, 0·2315M, in the solvent also containing methyl phenylcarbamate, 0·2314 g.-mol./l.

Time, mins.	0	20	118	297	1358	5640
Ph·NCO, g.-mol./l.	0·2315	0·2310	0·2306	0·2294	0·2200	0·2067

Hence, any reaction with the product is negligible over the normal period of experiments.

(*b*) A solution containing 0·2425 g.-mol./l. of pure methyl alcohol and 0·2397 g.-mol./l. of methyl phenylcarbamate in di-*n*-butyl ether was kept in a thermostat at 20° and any phenyl *iso*cyanate formed was determined, at intervals, on 10-ml. samples.

Time, mins.	5	495	795	2370
0·526N-NaOH required, ml.	0·370	0·345	0·350	0·345
Normal blank, ml.*	0·375	0·360	0·360	0·355

* The slight variation in the "blank" figures is due to the use of freshly prepared piperidine solutions at intervals throughout the experiment.

Velocity Determinations.—Examination of the residual reaction mixture after completion of a run showed the presence of only methyl phenylcarbamate as the reaction product, contaminated with only a trace of carbanilide. The introduction of slight traces of water vapour is almost unavoidable during the taking of samples, but the standard technique described below reduced the amount of carbanilide formed to negligible proportions.

The reaction vessel consisted of a long-necked flask fitted with a ground-in stopper half-way down the neck. The stopper was attached to a long glass handle closed at the top by a rubber cork fitting into the neck of the flask. The reaction vessel could thus be immersed to the level of the stopper in the thermostat so that the whole vessel was at constant temperature. All graduated flasks and reaction vessels were well dried, first at 110° in an electric oven and then in a vacuum desiccator over phosphoric oxide. Long tubular desiccators, containing calcium chloride and large enough to contain the graduated flasks, were immersed in the thermostat so that the flasks and solutions were kept in a dry atmosphere whilst they were attaining temperature equilibrium in the thermostat. Solutions of pure methyl alcohol of appropriate concentration, with or without the addition of a tertiary base catalyst, in di-*n*-butyl ether were made up in graduated flasks by using a weight pipette, and adjusted to the mark in the thermostat after temperature equilibrium was attained. A similar solution of the aryl *iso*cyanate (freshly distilled over phosphoric oxide directly into the dry weight pipette) was also prepared. The methyl-alcoholic solution (25 ml.) and solvent (50 ml.) were pipetted into the reaction vessel in the thermostat and, after attainment of temperature equilibrium, 25 ml. of the *iso*cyanate solution were added to start the reaction. All pipetting was carried out by use of suction through drying tubes from a water pump. At intervals, a 10-ml. sample was run directly into a mixture of 10 ml. of di-*n*-butyl ether and 5 ml. of the freshly-prepared standard piperidine solution, previously cooled to 0°, and the flask stoppered and kept at 0° for 15 mins. Constant-boiling alcohol (15 ml.) was added, followed by 10 ml. of 0·526N-hydrochloric acid in constant-boiling alcohol, four drops of the indicator added, and the excess acid was back-titrated with 0·526N-sodium hydroxide solution by a semi-microburette, to the first appearance of *bright* green colour. A blank determination was carried out each time fresh piperidine solution was used. All volumetric apparatus was calibrated to N.P.L. standard. All determinations are at 20°.

Uncatalysed reactions. The value of the velocity coefficient for the uncatalysed reaction was determined from the slope of the straight line obtained by plotting $\log_{10} b(a-x)/a(b-x)$ or (for equal initial concentrations) $x/(a-x)$ against time for the early stages of the reaction before any catalysis by the product formed caused deviation from the straight-line relationship. The results are tabulated below. In all cases the number of observations used in plotting the reaction-velocity curves are given in parentheses after each value of k_2.

[MeOH], g.-mol./l.	0·2350	0·2350	0·2399	
[Ph·NCO], g.-mol./l.	0·2774	0·2774	0·2399	
$10^3k_2^{20°}$, g.-mol.$^{-1}$ l.min.$^{-1}$	0·173(6)	0·168(6)	0·172(6)	Mean: 0·170

Catalytic effect of added methyl phenylcarbamate. The experiments were repeated with the addition of varying initial concentrations of methyl phenylcarbamate. With approximately equimolecular proportions of added product the plot for a second-order reaction rapidly became convex to the time axis, since the total concentration of urethane rapidly increased as the reaction proceeded. The recorded values of 10^3k_2 were those obtained for the initial stages of the reaction. With larger initial concentrations of added urethane the second-order plot remained a straight line over a large portion of the reaction, since the urethane formed during the reaction had only a small effect on the total urethane concentration present. The results are tabulated below:

[MeOH], g.-mol./l.	0·240	0·2386	0·2386
[Ph·NCO], g.-mol./l.	0·240	0·2386	0·2386
[NHPh·CO_2Me], g.-mol./l.	0·240	0·4772	0·6561
$10^3k_2^{20°}$, g.-mol.$^{-1}$l. min.$^{-1}$	0·263(4)	0·317(8)	0·355(7)

The correlation of these results with the expression for an autocatalysed reaction has already been noted (p. 714).

Reactions catalysed by tertiary bases. (*a*) Triethylamine. In the presence of varying concentrations of this tertiary base the procedure was the same except that 15 ml. of hydrochloric acid were used in the determination of the *iso*cyanate and a new blank was determined in the presence of the same concentration of triethylamine as was used in the experiment. The results obtained with varying concentrations of triethylamine are summarised below.

[MeOH], g.-mol./l.	0·2315	0·2315	0·2320	0·2320
[Ph·NCO], g.-mol./l.	0·2316	0·2316	0·2404	0·2360
[NEt_3], g.-mol./l.	0·2158	0·1079	0·0610	0·0306
$10^3k_2^{20°}$, g.-mol.$^{-1}$l. min.$^{-1}$	157(2)	80·9(6)	47·5(9)	22·9(9)

Effect of varying the molecular ratio MeOH/Ph·NCO *with catalysis by* 0·0305M-*triethylamine.*

[MeOH], g.-mol./l.	[Ph·NCO], g.-mol./l.	Ratio [MeOH]/[Ph·NCO].	$10^3k_2^{20°}$.
0·2380	0·2380	1	22·9(8)
0·2380	0·1190	2	22·1(7)
0·1190	0·2380	0·5	22·1(8)
0·4941	0·1241	4	19·0(6)

In the presence of a constant concentration of triethylamine the reaction thus stimulates a second-order one.

(*b*) Pyridine, α-picoline, quinoline, and diethylaniline, etc. With the weaker tertiary bases the base catalyst had no effect on the acid–alkali titre in the determination of the *iso*cyanate, and the standard technique was used.

	Pyridine.		α-Picoline.		Quinoline.		Diethylaniline.			
[MeOH], g.-mol./l.	0·2419	0·2419	0·2424	0·2424	0·2420	0·2420	0·2433	0·2422	0·2433	0·2426
[Ph·NCO], g.-mol./l.	0·2420	0·2410	0·2424	0·2424	0·2420	0·2420	0·2434	0·2422	0·2434	0·2426
[Base, g.-mol./l. ...	0·0306	0·0612	0·0306	0·0612	0·0306	0·0612	0·0306	0·0306	0·0612	0·0306 *
$10^3k_2^{20°}$, g.-mol.$^{-1}$/l. min.$^{-1}$	1·88(9)	3·57(9)	2·00(8)	3·99(8)	1·04(9)	1·98(9)	0·17(8)	0·175(7)	0·19(7)	0·20(9)

* With dimethylaniline.

Reactions with substituted aryl isocyanates (ArNCO). The applicability of the method for the determination of the aryl *iso*cyanate was tested with each derivative and a straight-line calibration curve was plotted for each. In all cases the determination gave 99—100% of the actual weight of pure *iso*cyanate added. The experimental data are summarised in the following table.

	Initial concentrations, g.-mol./l.			10^3k_2 (mean),	
Ar.	Ar·NCO.	MeOH.	NEt_3.	g.-mol.$^{-1}$ l.min.$^{-1}$.	No. of observtns.
p-Me·C_6H_4	0·2392	0·2394	0·0306	12·25	8
,,	,,	,,	0·0612	24·1	7
p-MeO·C_6H_4	0·2398	0·2399	0·0306	9·86	7
,,	,,	,,	0·0612	18·8	8
p-NO_2·C_6H_4 *	0·1602	0·1838	0·0291	2320	1
,,	0·1802	0·1980	0·0005	56·9	6
cyclo-C_6H_{11}	0·2424	0·2424	0·0306	0·021	5
,,	,,	,,	0·0612	0·043	4

* Determination difficult owing to great speed of reaction and very sparing solubility of urethane product.

We wish to thank Messrs. Imperial Chemical Industries Ltd., Dyestuffs Division, for facilities which have enabled this work to be carried out, and Dr. G. S. Rushbrooke, Brotherton Lecturer in Physical Chemistry, for mathematical assistance.

The University, Leeds, 2. [*Received, September 11th*, 1946.]

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136. *New Potential Chemotherapeutic Agents. Part VI. Derivatives of* 1 : 3-*Diaza-acridine.*

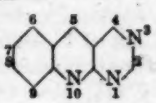
By F. E. King and T. J. King.

A series of dihydroxypyrimidines has been prepared with basic substituents at the 2- or the 4-position. In general, these were obtained from 2 : 4 : 6-trichloropyrimidine, with which the simple aliphatic amines gave isomeric dichloroaminopyrimidines. Hydrolysis of the chlorine in these compounds was conveniently carried out through the intermediate aminodibenzyloxy-derivatives, which were then debenzylated by catalytic hydrogenation.

The resulting aminodihydroxypyrimidines were condensed with *o*-aminobenzaldehyde; those with primary or secondary 2-amino-groups gave 2-amino-4-hydroxy-1 : 3-diaza-acridines (II; R = amino, R′ = OH). In the 4-amino-series, only the 4-guanidino-compound led to a basically substituted diaza-acridine; in the other condensations investigated, through hydrolysis of the basic side chains, the product was invariably 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH).

Reference has already been made (Part V, J., 1946, 681) to the interest, from the standpoint of chemotherapy, of compounds having a structural resemblance to riboflavin: mepacrine, acriflavine, and several other aminoacridines are examples of substances which may derive their biological activity from this connexion. Closely related to acridine, but having more features in common with the ring-system present in riboflavin, is another heterocyclic nucleus, (I), usually known as quinolino-2′ : 3′-4 : 5-pyrimidine, but more concisely designated 1 : 3-diaza-acridine. Compounds of this series have so far received little attention, and the literature records but one example, *i.e.*, the dihydroxy-derivative (II; R = R′ = OH). This was prepared by Conrad and Reinbach (*Ber.*, 1901, **34**, 1341) from *o*-aminobenzaldehyde and barbituric acid, a method apparently capable of adaptation to the synthesis of various other derivatives of the nucleus. Attempts have now been made to extend it to the preparation of 1 : 3-diaza-acridines with basic side-chains. The experiments outlined in the present paper concern diaza-acridines substituted at the 2- or the 4-position, as these can be derived from

relatively accessible 2- or 4-substituted pyrimidines. The 5-aminodiaza-acridines, through which analogues of mepacrine would be available, obviously cannot be obtained by the Conrad–Reinbach method, and it is hoped that a later publication will deal with this aspect of the work.



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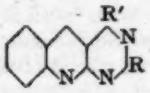

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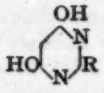

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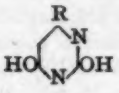
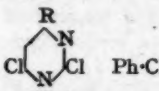


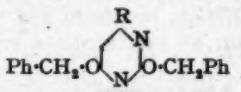
(IV.)

Initially, interest centred on derivatives containing the dialkylaminoalkylamine type of substituent, *e.g.* (II; R = NH·[CH$_2$]$_3$·NEt$_2$, R′ = OH). The heterocyclic component necessary for the synthesis of this diaza-acridine is 2-*γ-diethylamino*-n-*propylamino*-4 : 6-*dihydroxypyrimidine* (III; R = NH·[CH$_2$]$_3$·NEt$_2$), which was obtained from 2-mercaptobarbituric acid (III; R = SH) by heating with γ-diethylamino-*n*-propylamine and lead hydroxide, or analogously, omitting the hydroxide, from the 2-methylthio-compound (III; R = SMe). The latter can be prepared from thiobarbituric acid and methyl sulphate in good yield (cf. Wheeler and Jamieson, *Amer. Chem. J.*, 1904, **32**, 345) if the methylation is carried out in sodium bicarbonate solution.

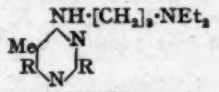
The synthesis of the isomeric pyrimidine (IV, R = NH·[CH$_2$]$_3$·NEt$_2$) was more difficult. Thus, the action of γ-diethylaminopropylamine on the ureide EtO$_2$C·CH$_2$·CO·NH·CO·NH$_2$ gave barbituric acid, and not the derivative Et$_2$N·[CH$_2$]$_3$·NH·CO·CH$_2$·CO·NH·CO·NH$_2$ (V), which might have cyclised to the required pyrimidine with phosphoryl chloride. An alternative route to (V) was unsuccessful, through failure of the *amido-ester* Et$_2$N·[CH$_2$]$_3$·NH·CO·CH$_2$·CH$_2$·CO$_2$Et to condense with urea, and the interaction of the corresponding *amidine* Et$_2$N·[CH$_2$]$_3$·NH·C(:NH)·CH$_2$·CO$_2$Et with ethyl carbamate—based on a synthesis of barbituric acid ("Friedländer," 1906, **8**, 1113)—gave complex products. Eventually, the required 4-*γ-diethylaminopropylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NH·[CH$_2$]$_3$·NEt$_2$) was obtained by starting from 2 : 4 : 6-trichloropyrimidine, which was prepared from barbituric acid by the method of Baddiley and Topham (*J.*, 1944, 678).



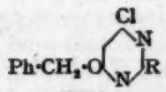
(VI.)



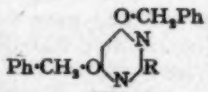
(VII.)



(VIII.)



(IX.)



(X.)

On adding γ-diethylaminopropylamine to a solution of the trichloropyrimidine in acetone, a crystalline *hydrochloride* separated in high yield. Analyses of this salt and of the *picrate* and *picrolonate* proved them to be derivatives of a dichlorodiethylaminopropylaminopyrimidine, which was later shown to be (VI; R = NH·[CH$_2$]$_3$·NEt$_2$), the basic substituent having entered the 4- (or equivalent 6-) position. In an attempt to convert it into the required dihydroxy-derivative, the compound was submitted to alkaline hydrolysis, but no alkali soluble product was obtained. On the other hand, concentrated hydrochloric acid at 100° led to the formation of a monochloro-base, isolated as a *hydrochloride*, which, on account of the greater reactivity of the 2-chlorine atom, is believed to be 6-chloro-4-γ-diethylaminopropylamino-2-hydroxy-pyrimidine [for a discussion relevant to this point, see Basford, Curd, and Rose (*J.*, 1946, 713].

Finally, the dichloroamine was converted into the related aminodibenzyloxypyrimidine (VII; R = NH·[CH$_2$]$_3$·NEt$_2$) so that an attempt might be made to remove the benzyl groups by hydrogenation. This method of hydrolysis does not seem previously to have been employed in the pyrimidine series, and a preliminary investigation was therefore carried out with 2 : 4 : 6-*tribenzyloxypyrimidine*, which was prepared from the trichloropyrimidine and sodium benzyloxide in boiling toluene. Hydrolysis of the benzyloxy-groups with sodium in liquid ammonia was unsuccessful, but, on hydrogenation over palladised charcoal, barbituric acid was obtained in excellent yield. When applied to (VII; R = NH·[CH$_2$]$_3$·NEt$_2$), the catalytic reduction method readily afforded a basically-substituted dihydroxypyrimidine which, being isomeric but not identical with that already prepared from 2-thio- or 2-methylthio-barbituric acid, was thus shown to be the 4-diethylaminopropylaminodihydroxy-compound (IV; R = NH·[CH$_2$]$_3$·NEt$_2$). The product coupled with *p*-chlorobenzenediazonium chloride, and an attempt was made to use the resulting p-*chlorobenzeneazopyrimidine* for a synthesis of 9-γ-diethyl-aminopropylxanthine, but, owing to the extreme readiness with which the intermediate diaminopyrimidine oxidised in the air, this intention was not realised.

The pyrimidine (IV; R = NH·[CH$_2$]$_3$·NEt$_2$) was tested for anti-malarial properties, but it

showed no activity against *P. gallinaceum* in chicks. However, in view of the activity of certain basically-substituted 5-methylpyrimidines—a property not apparent in lower homologues from which the methyl group is omitted (Hall, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357)—the 5-methyl analogue of (IV; R = NH·[CH_2]$_3$·NEt_2) was also synthesised. 2 : 4 : 6-Trichloro-5-methylpyrimidine combined with γ-diethylaminopropylamine to give a *hydrochloride*, presumably, by analogy with the previous condensation, a salt of 2 : 6-*dichloro*-4-*amino*-5-*methylpyrimidine* (VIII; R = Cl). From the derived *dibenzyloxy*-compound (VIII; R = O·CH_2·Ph), 4-γ-diethylamino-2 : 6-dihydroxy-5-methylpyrimidine (VIII, R = OH) was obtained by catalytic reduction, and characterised by a *picrate* and *picrolonate*. Like the pyrimidine (IV; R = NH·[CH_2]$_3$·NEt_2), when tested in a similar manner the product (VIII; R = OH) was found to have no antimalarial activity.

Before going on to the synthesis of the diethylaminopropylaminodiaza-acridines from the new pyrimidines, the preparation of some simpler aminodihydroxypyrimidines was first investigated, including 2-*methylamino*- and 2-*dimethylamino*-4 : 6-*dihydroxypyrimidine*, and 4-*methylamino*-, 4-*dimethylamino*-, and 4-*guanidino*-2 : 6-*dihydroxypyrimidine*.

The isomeric dichloromethylaminopyrimidines have already been prepared and oriented (Winkelmann, *J. pr. Chem.*, 1927, **115**, 292). Of these, the 2 : 6-dichloro-4-methylamino-compound (VI; R = NHMe) was directly converted into the corresponding *dibenzyloxy*-derivative (VII; R = NHMe), but the 4 : 6-dichloropyrimidine gave first 4-*chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (IX; R = NHMe), and further heating with the sodium benzyloxide was necessary to obtain the 2-*methylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NHMe). Catalytic reduction of the isomeric dibenzyloxypyrimidines occurred without difficulty to give the methylaminodihydroxy-compounds (III and IV; R = NHMe). Both are mentioned in patent literature (see *Chem. Zentr.*, 1938, I, 2790; II, 3163) but neither their preparation nor properties have been described.

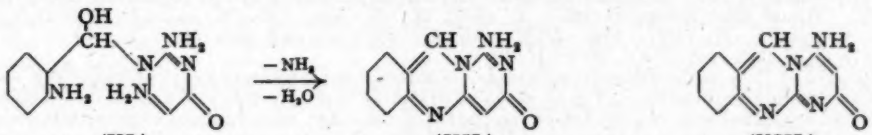
The action of dimethylamine on trichloropyrimidine in aqueous ethanol also gave two products of very markedly different solubilities, of which the sparingly soluble isomer, by analogy with the monomethylamine series, is regarded as the *dichloro*-4-*dimethylamino*-compound (VI; R = NMe_2). Both the 2-*dimethylamino*-4 : 6-*dichloropyrimidine* and its isomer (VI; R = NMe_2) gave *dibenzyloxypyrimidines* (VII and X; R = NMe_2), but from the somewhat less reactive 2 : 6-dichloro-compound it was possible to obtain an intermediate *monochloro*-*benzyloxypyrimidine* (IX; R = NMe_2).

Addition of trichloropyrimidine to guanidine in ethanol solution gave an oily product, apparently a mixture of dichloroethoxy- and chlorodiethoxy-pyrimidine, an unexpected result which may be connected with the high basicity of guanidine. With acetone as solvent, a dichloromonoguanidinopyrimidine separated, and as it is characteristic of the 4-amino-compounds in this series to be the less-soluble isomers, it was tentatively assigned the constitution (VI; R = NH·C[:NH]·NH_2). However, as in the trichloropyrimidine–diethylaminopropylamine condensation, none of the isomeric 2-guanidino-compound was found in the acetone residues. In the reaction with sodium benzyloxide in toluene a sparingly soluble product crystallised which is probably 6-*chloro*-4-*guanidino*-2-*benzyloxypyrimidine*. The dibenzyloxy-derivative formed on prolonged reaction and characterised by its *picrate*, was hydrogenated to give 4-*guanidino*-2 : 6-*dihydroxypyrimidine* (IV; R = NH·C[:NH]·NH_2). Its extremely sparing solubility in ethanol, in which respect it evidently differs from the 2-guanidinopyrimidine synthesised from ethyl malonate and diguanidine (Rackmann, *Annalen*, 1910, **376**, 176), is further evidence in support of its constitution and that of the dichloro-compound from which it is derived.

With the exception of the pyrimidine (IV; R = NH·C[:NH]·NH_2) the behaviour of the foregoing amino-compounds when condensed with *o*-aminobenzaldehyde conformed to the structures which have been assigned to them. The reaction conditions were first explored with 2- and 4-aminodihydroxypyrimidine and 2 : 4-diamino-6-hydroxypyrimidine. The condensations were carried out in aqueous solution, but, without the addition of acid, the pyrimidine 5-position is insufficiently activated for reaction to occur. With the addition of dilute hydrochloric acid, no difficulty was experienced in obtaining from malonylguanidine (III; R = NH_2) the expected 2-*amino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NH_2, R′ = OH), which was isolated first as a *hydrochloride*. On the other hand, in condensations involving the 4-amino-series of hydroxypyrimidines, mineral acid cannot be used owing to hydrolysis of the amino-group (see Conrad, *Annalen*, 1905, **340**, 312), and the reaction of 4-amino-2 : 6-dihydroxy-pyrimidine with *o*-aminobenzaldehyde was therefore carried out in aqueous acetic acid. The product exhibited the characterstic diaza-acridine fluorescence, but investigation showed it to

consist of 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = OH, R′ = OH), indicating the loss at some stage of the reaction of a molecule of ammonia. In view of the mild conditions, hydrolysis of the aminopyrimidine was unlikely, and it therefore appeared that ring-closure had occurred by loss of the 4-amino-group as ammonia in preference to the elimination of the hydroxyl at the 6-position. In order to demonstrate the possibility of such a reaction mechanism, *o*-aminobenzaldehyde was treated under similar conditions with 4 : 6-diamino-2-hydroxy- and 2 : 4 : 6-triamino-pyrimidine, but in neither case could any condensation be induced.

Elimination of ammonia also occurred in the reaction between 2 : 4-diamino-6-hydroxypyrimidine and *o*-aminobenzaldehyde, which gave a deep yellow, sparingly soluble compound. This had the molecular composition of the aminohydroxydiaza-acridines, but was clearly different from the base (II; R = NH_2, R′ = OH) already prepared from malonylguanidine. On the other hand, it appeared incredible that the new substance could be the isomeric 4-amino-2-hydroxydiaza-acridine, since its formation would have necessitated the loss of the stable 2-amino-group of the pyrimidine while retaining the more readily hydrolysable 4-substituent. It is much more probable that, the pyrimidine 5-position being insufficiently active, the primary reaction of the aldehyde group is to combine with one of the two hetero atoms forming a carbinol (XI). Ring-closure, by extrusion of ammonia, would then lead to a



(XI.) (XII.) (XIII.)

new type of diaza-acridine, and of the two possible products (XII) and (XIII), preference is given to 4-*amino*-2-*keto*-3 : 12-*diaza*-2 : 12-*dihydroacridine* (XII) (or its 2-hydroxy-4-imino-tautomer) which would be obtained by removal of the more labile 4-amino-group. A further alternative, in which the 2- and 4-substituents of (XII) are interchanged, can also be dismissed since the initial carbinol formation is unlikely to take place with the nuclear amido-nitrogen in preference to that which is part of an amidine structure.

Condensation of 2-methylamino-4 : 6-dihydroxypyrimidine with *o*-aminobenzaldehyde gave the expected 2-*methylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NHMe, R′ = OH), but, as anticipated from the behaviour of the corresponding primary amine (IV; R = NH_2), the isomeric 4-methylaminodihydroxypyrimidine, by undergoing loss of methylamine, yielded the dihydroxydiaza-acridine (II, R = R′ = OH). The two dimethylaminodihydroxypyrimidines, in which triketo-tautomerism is excluded by the tertiary nature of the amino-groups, both failed to react with the aldehyde, and it is of interest in this connexion that the 4-dimethylamino-group in the pyrimidine (IV; R = NMe_2) is not hydrolysed by boiling hydrochloric acid. Somewhat remarkably, in view of previous failures to synthesis 4-aminodiaza-acridines, the 4-guanidinodihydroxypyrimidine easily condensed with *o*-aminobenzaldehyde in 25% acetic acid, to give the 4-*guanidinohydroxydiaza-acridine* (II, R = OH, R′ = NH·C[:NH]·NH_2), which was further characterised by the *hydrochloride* and *picrate*. It is suggested that this exceptional result can be interpreted in terms of the enhanced stability conferred on the guanidino kation by resonance.

Finally, the diethylaminopropylaminodihydroxypyrimidines were condensed with aminobenzaldehyde, the 2-isomer affording 2-*γ-diethylaminopropylamino*-4-*hydroxy*-1 : 3-*diaza-acridine*. Tested in the form of a *meconate*, it proved inactive against *P. gallinaceum* infections in chicks. Condensation of the 4-aminopyrimidine (IV; R = NH·$[CH_2]_3$·NEt_2) was accompanied by loss of the basic side-chain, the product once more being the diaza-acridine (II; R = R′ = OH).

The possibility of introducing amino-groups into the benzene ring of the diaza-acridines was considered, and for this purpose 2 : 4-dinitrobenzaldehyde, which gave with barbituric acid a *benzylidene* derivative, was prepared. The 4-nitro-2-amino-aldehyde obtained by ferrous hydroxide reduction condensed with barbituric acid to give 8-*nitro*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*, but this compound is so sparingly soluble that it has not been possible to bring about reduction of the 8-nitro-group.

Through the kindness of Dr. E. P. Abraham of the Sir William Dunn School of Pathology, Oxford, the above diaza-acridines were examined for antibacterial properties. With the exception of the 2-amino-4-hydroxy-derivative, which is slightly active, none of them showed antibacterial activity when tested *in vitro* against *Staph. aureus*. For the antimalarial tests

recorded above we are indebted to Miss I. M. Tonkin, National Institute of Medical Research, London, N.W.3.

Experimental.

2-γ-Diethylaminopropylamino-4 : 6-dihydroxypyrimidine (III; R = NH·[CH$_2$]$_3$·NEt$_2$).—(*a*) Mercaptor barbituric acid (5 g.), γ-diethylaminopropylamine (4·5 g., 1·5 mol.), and freshly prepared lead hydroxide (*ca.* 2 mols.) were heated in refluxing *iso*amyl alcohol for 15 hours. The hot solution was filtered and evaporated under reduced pressure, giving a friable mass (6·5 g., 78%), which was identified as the amine (III; R = NH·[CH$_2$]$_3$·NEt$_2$) by its picrolonate (below).

(*b*) Mercaptobarbituric acid (14·4 g.) in aqueous sodium bicarbonate (8·4 g. in 200 c.c. of water) was shaken at room temperature with methyl sulphate (12·6 g.); after 30 minutes the sulphate had dissolved and a crystalline solid had separated. This was collected, washed with water, alcohol, and ether, and identified as 4 : 6-dihydroxy-2-methylthiopyrimidine (10·4 g., 72%) (cf. Wheeler and Jamieson, *loc. cit.*).

Without further purification the methylated pyrimidine (10 g., 1 mol.) was gradually heated to 180° with γ-diethylaminopropylamine (3·9 g., 0·95 mol.); the nearly solid mass then became gummy and methylthiol was evolved. After 30 minutes reaction ceased, and the mixture was cooled, dissolved in ethanol (70 c.c.), filtered to remove unchanged pyrimidine, and evaporated under reduced pressure. The product (13 g., 92%) was soluble in water and ethanol, sparingly soluble in ether. Its hydrochloride, oxalate, and picrate were oily, but the *picrolonate*, prepared in acetone, crystallised after 24 hours at 0°. It separated from *cyclo*hexanone–ether as a hydrate in microscopic yellow tablets, m. p. 235° (decomp.) (Found: C, 47·7; H, 5·5; N, 20·9. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,H_2O$ requires C, 48·3; H, 5·7; N, 21·4%. Found after drying at 100°: C, 48·9; H, 5·5; loss, 1·85. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,\frac{1}{2}H_2O$ requires C, 49·1; H, 5·6; loss, 1·7%. Found after drying at 150°: C, 49·8; H, 5·4. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4$ requires C, 50·0; H, 5·6%).

Carbethoxyacet-(N-γ-diethylaminopropyl)amide.—Solutions of carbethoxyacetyl chloride (6 g., 1 mol.) and γ-diethylaminopropylamine (5·2 g., 1 mol.) in dry ether were gradually mixed at 0°. The orange oil which had separated was treated, after decantation of the ether, with aqueous sodium carbonate, and the liberated base taken up in chloroform. By distillation the *amido-ester* was obtained as a colourless oil (5·85 g., 60%), b. p. 115°/0·05 mm. (Found: C, 59·3; H, 9·9; N, 12·2. $C_{12}H_{24}O_3N_2$ requires C, 59·0; H, 9·8; N, 11·5%). When it was heated with sodium ethoxide and urea in ethanol for 6 hours, a thick black oil was obtained, distillation of which gave no recognisable new product.

An attempt to prepare the corresponding acid from ethyl carboxyacetate and γ-diethylaminopropylamine was unsuccessful, and hydrolysis of the amido-ester with aqueous alcoholic potassium hydroxide (1 mol.) at room temperature gave an oil, which on treatment with picrolonic acid gave only the γ-diethylaminopropylamine salt.

Carbethoxyacet-(N-γ-diethylaminopropyl)amidine.—Ethyl α-carbethoxyacetiminate hydrochloride (6 g., 1 mol.) in ethanol (100 c.c.) was treated with γ-diethylaminopropylamine (4·2 g., 1 mol.) at room temperature. Heat was evolved, and after 12 hours the solvent was evaporated under reduced pressure to give a colourless oil, from which the *picrolonate*, prepared in acetone solution, was obtained without further crystallisation in an analytically pure condition as yellow prisms, m. p. 125—130° (Found: C, 48·6; H, 5·5; N, 19·0; loss on drying at 100°, 2·8. $C_{12}H_{24}O_3N_2,2C_{10}H_8O_5N_4,H_2O$ requires C, 48·7; H, 5·7; N, 19·5; loss, 2·3%).

Attempts to condense the amidine with ethyl carbamate in the presence of sodium ethoxide gave complex oily products. The only crystalline derivative obtained from these oils was γ-diethylaminopropylamine picrolonate. Later, when the properties of the desired compound (IV; R = NH·[CH$_2$]$_3$·NEt$_2$) were known it became certain that it could not have been present in the reaction mixture.

2 : 4 : 6-*Tribenzyloxypyrimidine.*—To powdered sodium (1·15 g., 1 mol.) under toluene (100 c.c.), benzyl alcohol (11 g., 2 mols.) was added, and after the initial vigorous reaction had subsided the mixture was heated under reflux until no more sodium remained (2 hours). When trichloropyrimidine (3 g., 1 mol.) in toluene (10 c.c.) was cautiously added, the thick mass of sodium benzyloxide rapidly disappeared and sodium chloride was deposited. After refluxing for 1 hour, the solution was cooled and shaken with water to remove sodium chloride and any remaining alcohol, and the toluene was evaporated under reduced pressure. The residual oil solidified on trituration with ethanol to give 2 : 4 : 6-*tribenzyloxypyrimidine* (4·1 g., 63%) which crystallised in long silky needles, m. p. 62—64°, soluble in alcohols, ether, and acetone, insoluble in water (Found: C, 75·3; H, 5·6; N, 6·9. $C_{25}H_{22}O_3N_2$ requires C, 75·4; H, 5·5; N, 7·0%).

Treatment with sodium in liquid ammonia gave a mixture of products from which no pure compound was obtained.

Barbituric Acid.—Tribenzyloxypyrimidine (2 g.) dissolved in acetic acid (40 c.c.) was hydrogenated at atmospheric pressure and temperature over palladised charcoal (0·1 g.). Reduction was complete in 2 hours, and on evaporating the filtered solution barbituric acid (0·54 g., 84%) was obtained and identified by its melting point and that of its benzylidene derivative.

2 : 6-*Dichloro-4-γ-diethylaminopropylaminopyrimidine* (VI; R = NH·[CH$_2$]$_3$·NEt$_2$).—By the method of Baddiley and Topham (*loc. cit.*), using pure dry barbituric acid and gently warming the reaction mixture until the solid passed into solution, trichloropyrimidine was obtained pure after one distillation in up to 83% yield. γ-Diethylaminopropylamine (13 g., 1 mol.) in acetone (50 c.c.) was cautiously added to an acetone solution of trichloropyrimidine (18 g., 1 mol., in 100 c.c.); the reaction vessel must be cooled during addition to prevent loss by frothing. On cooling, and with vigorous scratching, the product separated as a crystalline mass. After 1 hour the solid was collected and washed with cold acetone (yield 22·6 g., 72%); by concentrating the mother liquors a further crop (4·1 g., total yield 85%) was obtained. Crystallisation from acetone gave the *hydrochloride* in colourless large glistening rhombs, m. p. 149° (Found: C, 42·2; H, 6·1; N, 18·1. $C_{11}H_{18}N_4Cl_2,HCl$ requires C, 42·1; H, 6·0; N, 17·6%). Aqueous solutions of the hydrochloride and sodium picrate gave the *picrate*, separating from ethanol in

bright yellow shining prisms, m. p. 162° (Found: C, 40·3; H, 4·4; Cl, 13·9. $C_{11}H_{18}N_4Cl_2,C_6H_3O_7N_3$ requires C, 40·3; H, 4·2; Cl, 14·0%). An alcoholic solution of the hydrochloride with picrolonic acid gave the *picrolonate*, which crystallised from *n*-propanol in yellow prisms, m. p. 164° (Found: Cl, 13·1. $C_{11}H_{18}N_4Cl_2,C_{10}H_8O_5N_4$ requires Cl, 13·1%).

Experiments on the hydrolysis of the dichloroaminopyrimidine by heating with aqueous alcoholic potassium hydroxide gave only alkali-insoluble products. These, on treatment with picric acid, gave mixed salts, among them the above picrate, m. p. 162°, but nothing corresponding to a dihydroxypyrimidine derivative could be isolated.

6-Chloro-4-γ-diethylaminopropylamino-2-hydroxypyrimidine.—The above dichloro-compound (3·1 g.) was digested on a steam-bath with concentrated hydrochloric acid (10 c.c.) for 12 hours. Evaporation of the solvent gave a residue consisting of a *dihydrochloride* (2·5 g., 76%), very soluble in water, sparingly so in alcohol and acetone. It separated from boiling ethanol in colourless platelets, m. p. 253° (decomp.) (Found: C, 39·6; H, 6·4; N, 16·7; Cl, 31·8. $C_{11}H_{19}ON_4Cl,2HCl$ requires C, 39·8; H, 6·3; N, 16·9; Cl, 32·1%). An aqueous solution of the hydrochloride treated with alcoholic picric acid gave the *picrate*, very sparingly soluble in ordinary solvents, and crystallising from a large volume of boiling water in small compact yellow tablets, m. p. 209° (decomp.) Found: C, 41·5; H, 4·5; Cl, 7·9. $C_{11}H_{19}ON_4Cl,C_6H_3O_7N_3$ requires C, 41·8; H, 4·5; Cl, 7·3%).

4-γ-Diethylaminopropylamino-2:6-dibenzyloxypyrimidine (VII; R = NH·$[CH_2]_3$·NEt_2).—To powdered sodium (1·4 g., 1 mol.) under toluene (100 c.c.), benzyl alcohol (13 g., 2 mol.) was added, and, when the sodium had reacted, 2:6-dichloro-4-γ-diethylaminopropylaminopyrimidine (6·25 g., 1 mol.) was introduced in 10 portions with shaking. The sodium benzyloxide rapidly disappeared with evolution of heat, after which the liquid was refluxed for 2 hours. After being washed with water, dried, and evaporated under reduced pressure, the toluene solution yielded a pale brown viscous oil which solidified on standing. Crystallisation from light petroleum gave the *benzyloxypyrimidine* (6·5 g., 80%) in colourless needles, m. p. 68° (Found: C, 71·0; H, 7·4; N, 13·3. $C_{25}H_{32}O_2N_4$ requires C, 71·4; H, 7·6; N, 13·3%). Its *dipicrate* was obtained from alcohol solution in large glistening prisms, m. p. 156° (Found: C, 50·1; H, 4·5; N, 16·0. $C_{25}H_{32}O_2N_4,2C_6H_3O_7N_3$ requires C, 50·6; H, 4·3; N, 16·0%).

4-γ-Diethylaminopropylamino-2:6-dihydroxypyrimidine (IV; R = NH·$[CH_2]_3$·NEt_2).—The crude benzyloxypyrimidine from 2:6-dichloro-4-γ-diethylaminopropylaminopyrimidine hydrochloride (12·5 g.), dissolved in acetic acid (75 c.c.), was hydrogenated over palladised charcoal at room pressure and temperature. After 4 hours, hydrogen uptake (1270 c.c., 71%) ceased, and the catalyst was removed and the solvent evaporated under reduced pressure. The product (10·2 g., 61%), a light brown oil, had partially crystallised after 1 month in a vacuum over potassium hydroxide, and was apparently the *acetate* (Found: C, 45·0; H, 8·0. $C_{11}H_{20}O_2N_4,3C_2H_4O_2$ requires C, 45·3; H, 7·8%). It was very hygroscopic, soluble in ethanol and acetone, insoluble in ether and light petroleum, and its alcoholic solution gave a *picrate* crystallising in small needles, m. p. 225° (decomp.) (Found: C, 43·4; H, 5·2; N, 20·5. $C_{11}H_{20}O_2N_4,C_6H_3O_7N_3$ requires C, 43·5; H, 4·9; N, 20·9%). From acetone the very sparingly soluble *picrolonate* was slowly deposited, which crystallised from dimethylformamide–ethanol in minute prisms, m. p. 186° (decomp.) (Found: C, 47·2; H, 5·8; N, 20·9. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,2H_2O$ requires C, 46·7; H, 5·9; N, 20·8%. Found after drying at 100°: C, 48·3; H, 6·0; N, 21·5. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4,H_2O$ requires C, 48·2; H, 5·7; N, 21·4%. Found after drying at 130°: C, 49·7; H, 5·8. $C_{11}H_{20}O_2N_4,C_{10}H_8O_5N_4$ requires C, 50·0; H, 5·6%).

4-γ-Diethylaminopropylamino-5-p-chlorobenzeneazo-2:6-dihydroxypyrimidine.—*p*-Chlorobenzenediazonium chloride, from *p*-chloroaniline (1·6 g., 1 mol.), in excess of hydrochloric acid, was added to an aqueous solution (100 c.c.) of the pyrimidine (IV; R = NH·$[CH_2]_3$·NEt_2) (5 g., 1 mol.), and the mixture neutralised with sodium bicarbonate. After 24 hours at 0° a bright yellow sludge had separated, from which the supernatant liquid and washings were removed by centrifugation. The product was digested with ethanol (100 c.c.) to remove a bright red soluble impurity, and the sparingly soluble residue crystallised from a large volume of alcohol. The pure *azopyrimidine* (2·7 g., 57%), separated in yellow feathery needles, m. p. 151° (efferv.) (Found: C, 49·2; H, 6·35; N, 19·9. $C_{17}H_{23}O_2N_6Cl,2H_2O$ requires C, 49·2; H, 6·4; N, 20·3%. Found after drying at 100°: Cl, 8·95. $C_{17}H_{23}O_2N_6Cl,H_2O$ requires Cl, 8·95%). From the purified base and alcoholic picric acid, the *dipicrate*, m. p. 205° (decomp.), was obtained (Found: C, 41·2; H, 3·7. $C_{17}H_{23}O_2N_6Cl,2C_6H_3O_7N_3$ requires C, 41·6; H, 3·5%).

Catalytic reduction of the azo-compound over Raney nickel gave a product which very rapidly oxidised in air. Immediate treatment of the reduction mixture with formic acid followed by removal of the catalyst, evaporation, and heating to 180°, gave an intractable tar.

2:6-Dichloro-4-γ-diethylaminopropylamino-5-methylpyrimidine (VIII; R = Cl).—2:4:6-Trichloro-5-methylpyrimidine (19·7 g., 1 mol.), which was obtained from 5-methylbarbituric acid in 76% yield by the method of Baddiley and Topham, was dissolved in acetone (100 c.c.) and cautiously treated with an acetone solution of γ-diethylaminopropylamine (13 g. 1 mol., in 100 c.c.). On cooling to 0°, the *hydrochloride* (15·4 g., 41%) separated, and concentration of the solution gave a further quantity (6·5 g., 20%). The salt, which is easily soluble in ethanol and highly soluble in water, was recrystallised from acetone, and it then formed large glistening tablets, m. p. 193—195° (Found: C, 44·2; H, 6·5; Cl, 33·2. $C_{12}H_{20}N_4Cl_2,HCl$ requires C, 43·7; H, 6·4; Cl, 32·6%). Treated with aqueous sodium picrate, it gave a *picrate*, which crystallised from a large quantity of alcohol in long prisms, m. p. 163° (Found: C, 41·2; H, 4·4; N, 18·5. $C_{12}H_{20}N_4Cl_2,C_6H_3O_7N_3$ requires C, 41·4; H, 4·4; N, 18·8%).

4-γ-Diethylaminopropylamino-2:6-dibenzyloxy-5-methylpyrimidine (VIII; R = O·CH_2Ph).—2:6-Dichloro-4-γ-diethylaminopropylamino-5-methylpyrimidine hydrochloride (8·2 g.) was slowly added to a suspension of sodium benzyloxide (from 1·72 g. of sodium) in toluene (75 c.c.), which was then heated under reflux for 2 hours. When isolated from the solvent, the dibenzyloxy-compound was an uncrystallisable oil which in ethanol solution gave a *tripicrate* having m. p. 141—142° not raised by recrystallisation from *iso*amyl alcohol (Found: C, 47·2; H, 3·9; N, 16·4. $C_{26}H_{34}O_2N_4,3C_6H_3O_7N_3$ requires C, 47·1; H, 3·8; N, 16·3%).

4-γ-Diethylaminopropylamino-2:6-dihydroxy-5-methylpyrimidine (VIII; R = OH).—The unpurified benzyloxypyrimidine from the above reaction was hydrogenated in acetic acid (100 c.c.) over palladised

charcoal at room temperature and pressure. Absorption (952 c.c., 85%) ceased after 5 hours; the filtered solution was then evaporated. The residue (7·2 g.), which partially solidified on leaving in a vacuum desiccator for a month, consisted of the *triacetate* (Found: C, 48·4; H, 8·2; N, 12·3. $C_{12}H_{22}O_3N_4,3C_2H_4O_2,H_2O$ requires C, 48·8; H, 8·1; N, 12·7%). From the acetate a sparingly soluble *dipicrate* was obtained as yellow needles, m. p. 183—184° (decomp.), from *iso*amyl alcohol (Found: C, 40·5; H, 4·1; N, 19·2. $C_{12}H_{22}O_3N_4,2C_6H_3O_7N_3$ requires C, 40·4; H, 3·9; N, 19·7%). The *picrolonate* was a yellow microcrystalline powder, m. p. 223° (decomp.) (Found: C, 50·7; H, 5·6. $C_{12}H_{22}O_3N_4,C_{10}H_8O_5N_4$ requires C, 50·9; H, 5·8%).

4-*Chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (IX; R = NHMe).—4 : 6-Dichloro-2-methylaminopyrimidine (Winkelmann, *loc. cit.*) (4·4 g., 1 mol.) was added to sodium benzyloxide (from 1·15 g. of sodium, 2 mols.) in toluene (150 c.c.), and after 1 hour at 100° the toluene was washed with water and evaporated. The residue, which solidified on trituration with alcohol, had no definite m. p., and presumably also contained the dibenzyloxypyrimidine (X; R = NHMe), but on crystallisation from ethanol 4-*chloro*-2-*methylamino*-6-*benzyloxypyrimidine* (1·7 g., 27·5%) was obtained as glistening colourless platelets, m. p. 120° (Found: N, 15·9; Cl, 14·9. $C_{12}H_{12}ON_3Cl$ requires N, 16·7; Cl, 14·2%).

2-*Methylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NHMe).—When similar quantities of the reagents used in the foregoing preparation of the pyrimidine (IX, R = NHMe) were heated in vigorously refluxing toluene (50 c.c.) for 4 hours, a more soluble product was obtained, from which 2-*methylamino*-4 : 6-*dibenzyloxypyrimidine* (5·5 g., 61%) was obtained on crystallisation from ethanol as colourless, long radiating spikes, m. p. 101° (Found: C, 71·2; H, 5·8; N, 13·2. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 5·9; N, 13·1%).

2-*Methylamino*-4 : 6-*dihydroxypyrimidine* (III; R = NHMe).—The reduction of 2-methylamino-4 : 6-dibenzyloxypyrimidine (5·0 g.) in acetic acid (75 c.c.) using palladised charcoal required 8 hours; hydrogen uptake (630 c.c. 90%) had then ceased. The slowness of the reaction appeared to be due to separation of the sparingly soluble product. It was dissolved by heating, and the filtered solution on cooling gave 2-*methylamino*-4 : 6-*dihydroxypyrimidine* (1·9 g., 66·6%). It dissolved in aqueous alkali and mineral acid, and being sparingly soluble in ethanol and water, was recrystallised from acetic acid, separating in compact prisms, m. p. > 310° (Found: C, 39·4; H, 5·6; N, 22·4. $C_5H_7O_2N_3,\frac{1}{2}C_2H_4O_2,\frac{1}{2}H_2O$ requires C, 39·4; H, 5·8; N, 23·0%. Found after drying at 100°: C, 42·2; H, 4·9; loss, 21·2. $C_5H_7O_2N_3$ requires C, 42·5; H, 5·0; loss, 23·0%).

4-*Methylamino*-2 : 6-*dibenzyloxypyrimidine* (VII; R = NHMe).—2 : 6-Dichloro-4-methylaminopyrimidine (Winkelmann, *loc. cit.*) (6 g.) was heated with sodium benzyloxide (from 1·55 g. of sodium) in boiling toluene (75 c.c.) for 3 hours. After evaporation of the washed and dried solution, the residue of 4-*methylamino*-2 : 6-*dibenzyloxypyrimidine* (7·45 g., 69%), which was quite soluble in cold alcohol, ether and acetone, was recrystallised from ethanol, separating as large colourless leaflets, m. p. 118° (Found: C, 70·8; H, 5·8; N, 12·8. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 5·9; N, 13·1%).

4-*Methylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NHMe).—4-Methylamino-2 : 6-dibenzyloxypyrimidine (6·45 g.), dissolved in acetic acid (60 c.c.), was almost completely hydrogenated with palladised charcoal catalyst under normal conditions within 2½ hours. Removal of catalyst and solvent gave the crystalline 4-*methylamino*-2 : 6-*dihydroxypyrimidine* (2·8 g., 98·8%), soluble in aqueous alkali and acid, very sparingly soluble in ethanol and water. It was recrystallised from acetic acid and formed minute tablets, m. p. 302° (decomp.) (Found: C, 42·8; H, 5·0; N, 30·2. $C_5H_7O_2N_3$ requires C, 42·5; H, 5·0; N, 29·8%).

2 : 6-*Dichloro*-4-*dimethylaminopyrimidine* (VI; R = NMe_2).—Trichloropyrimidine (15 g., 1 mol.) in ethanol (75 c.c.) was treated with aqueous dimethylamine (27 c.c. of 33%, 2·5 mol.); 2 : 6-*dichloro*-4-*dimethylaminopyrimidine* (7·5 g., 48%) slowly separated. The base was insoluble in water, sparingly soluble in cold acetone and alcohol, and crystallised from alcohol in long colourless needles, m. p. 113° (Found: C, 38·0; H, 3·8; Cl, 37·0. $C_6H_7N_3Cl_2$ requires C, 37·5; H, 3·6; Cl, 36·9%).

4-*Dimethylamino*-2 : 6-*dibenzyloxypyrimidine* (VII; R = NMe_2).—When 2 : 6-dichloro-4-dimethylaminopyrimidine (7 g.,) and sodium benzyloxide (from 1·68 g. of sodium) were refluxed in toluene (75 c.c.) for an hour, the *dibenzyloxypyrimidine* (VII; R = NMe_2) was obtained. Isolated in the usual way, it crystallised from ethanol in beautiful long needles (8·5 g., 69·5%), m. p. 79° (Found: C, 71·3; H, 6·6; N, 11·9. $C_{20}H_{21}O_2N_3$ requires C, 71·6; H, 6·3; N, 12·5%).

4-*Dimethylamino*-2 : 6-*dihydroxypyrimidine* (IV; R = NMe_2).—The above dibenzyloxypyrimidine (7 g.) was completely hydrogenated over palladised charcoal in acetic acid (75 c.c.) under normal conditions within 4 hours. Removal of catalyst and solvent gave the *dihydroxy*-compound (IV; R = NMe_2), a sparingly soluble solid of amphoteric character, which crystallised from acetic acid in large colourless tablets (2·5 g., 77%), m. p. 320° (efferv.) (Found: C, 46·7; H, 6·0. $C_6H_9O_2N_3$ requires C, 46·5; H, 5·8%). After being boiled for 1 hour with dilute hydrochloric acid, the base was recovered unchanged on neutralisation.

4 : 6-*Dichloro*-2-*dimethylaminopyrimidine*.—When water (150 c.c.) was added to the alcoholic mother liquors from the preparation of 2 : 6-dichloro-4-dimethylaminopyrimidine (VI; R = NMe_2), an oil separated which solidified on scratching. It was very soluble in cold alcohol and acetone, but recrystallisation from aqueous ethanol gave the 2-*dimethylamino*-compound (5·5 g., 35%), m. p. 102—103° (Found: C, 37·9; H, 3·7; Cl, 37·6. $C_6H_7N_3Cl_2$ requires C, 37·5; H, 3·6; Cl, 36·9%).

4-*Chloro*-2-*dimethylamino*-6-*benzyloxypyrimidine* (IX; R = NMe_2).—4 : 6-Dichloro-2-dimethylaminopyrimidine (3·5 g., 1 mol.) and sodium benzyloxide (from 0·84 g. of sodium, 2 mols.), heated in toluene (50 c.c.) to 100° for an hour, gave, on isolation in the usual way, a solid residue from which the *monobenzyloxy*-compound (3·5 g., 73%) was obtained. It crystallised from alcohol in long colourless rods, m. p. 84° (Found: C, 59·0; H, 5·2; Cl, 13·9. $C_{13}H_{14}ON_3Cl$ requires C, 59·2; H, 5·3; Cl, 13·5%).

2-*Dimethylamino*-4 : 6-*dibenzyloxypyrimidine* (X; R = NMe_2).—When 4 : 6-dichloro-2-dimethylaminopyrimidine (7 g.) and sodium benzyloxide (from 1·68 g. of sodium) were heated in toluene (100 c.c.) under reflux for 3 hours, and the washed solution evaporated, an uncrystallisable oil (8·5 g., 69·5%) was obtained. Treatment with alcoholic picric acid gave the *picrate*, pure after one crystallisation from

ethanol; it formed yellow leaflets, m. p. 176° (Found: C, 55·7; H, 4·3. $C_{20}H_{21}O_2N_3,C_6H_3O_7N_3$ requires C, 55·3; H, 4·2%).

2-Dimethylamino-4 : 6-dihydroxypyrimidine (III, R = NMe_2).—2-Dimethylamino-4 : 6-dibenzyloxypyrimidine (6·5 g.) was hydrogenated in acetic acid solution (100 c.c.) over palladised charcoal under normal conditions during 5 hours. Evaporation of the filtered solution under reduced pressure gave the *dihydroxypyrimidine* (III, R = NMe_2), which crystallised from acetic acid in stout yellowish prisms (2·2 g., 73%), m. p. 320° (efferv.) Found: C, 46·0; H, 5·7; N, 27·9. $C_6H_9O_2N_3$ requires C, 46·5; H, 5·8; N, 27·1%). The pyrimidine was very sparingly soluble in water, but dissolved in aqueous acid and alkali.

2 : 6-Dichloro-4-guanidinopyrimidine [VI; R = NH·C(:NH)·NH_2].—Guanidine, prepared from guanidine hydrochloride (6 g., 2 mols.), in water (10 c.c.) was added to a solution of trichloropyrimidine (5·75 g., 1 mol.) in acetone (90 c.c.). Heat was evolved, and after 15 minutes a colourless crystalline solid separated, which was collected, washed with acetone, and dried. The *dichloroguanidinopyrimidine* (3·4 g., 53%), which was insoluble in water and very sparingly soluble in acetone and alcohol, crystallised from alcohol in long colourless needles, m. p. 325° (decomp., previous darkening) (Found: C, 29·5; H, 2·5; Cl, 34·4. $C_5H_3N_5Cl_2$ requires C, 29·1; H, 2·4; Cl, 34·5%). On adding water to the residual acetone solution, a further quantity (up to 43%) of the apparently identical product, having the same exceptionally high m. p., was obtained; there was no evidence that any significant amount of a 2-guanidino-compound was present in the solution.

6-Chloro-4-guanidino-2-benzyloxypyrimidine.—2 : 6-Dichloro-4-guanidinopyrimidine (2·1 g., 1 mol.) was heated with sodium benzyloxide (from 0·46 g. of sodium, 2 mols.) in toluene (50 c.c.) to 100° for 2 hours. The insoluble product was collected, washed with water, and crystallised from ethanol; the *6-chloro-4-guanidino-2-benzyloxypyrimidine* (1·7 g., 61%) was thus obtained in colourless needles, very sparingly soluble in cold toluene, m. p. 170° (Found: C, 51·8; H, 4·5. $C_{12}H_{12}ON_5Cl$ requires C, 51·9; H, 4·3%). Treatment with ethanolic picric acid gave a *picrate* which crystallised from *iso*amyl alcohol in small yellow prisms, m. p. 250° (decomp.) (Found: Cl, 7·3. $C_{12}H_{12}ON_5Cl,C_6H_3O_7N_3$ requires Cl, 7·0%).

4-Guanidino-2 : 6-dibenzyloxypyrimidine [VII; R = NH·C(:NH)·NH_2].—2 : 6-Dichloro-4-guanidinopyrimidine (5 g.) was heated with sodium benzyloxide (from 1·1 g. of sodium) in refluxing toluene (75 c.c.) for 8 hours. The semi-solid yellow oil (6·6 g., 78%), which was subsequently isolated, was difficult to recrystallise, and so the dibenzyloxypyrimidine was characterised by its *picrate*, which separated from *iso*amyl alcohol as microscopic prisms, m. p. 200° (Found: C, 51·5; H, 4·0; N, 19·8. $C_{19}H_{19}O_2N_5,C_6H_3O_7N_3$ requires C, 51·8; H, 3·8; N, 19·4%).

4-Guanidino-2 : 6-dihydroxypyrimidine [IV; R = NH·C(:NH)·NH_2].—Hydrogenation of the unpurified 4-guanidino-2 : 6-dibenzyloxypyrimidine (4·1 g.) in acetic acid (125 c.c.) over palladised charcoal ceased in 5 hours, by which time a finely divided solid had separated. This dissolved on heating, and after filtration the solvent was removed under reduced pressure. The crude solid, which was very sparingly soluble in water, ethanol, and *iso*amyl alcohol, readily dissolved in hot acetic acid with which it formed a gel on cooling. The total product was finally treated with boiling water (1 l.), the insoluble fraction discarded, and the filtered solution evaporated. The residue (0·8 g., 38%) consisted of the *guanidinopyrimidine* [IV; R = NH·C(:NH)·NH_2], m. p. 300° (Found: C, 33·6; H, 4·4. $C_5H_7O_2N_5,\frac{1}{2}H_2O$ requires C, 33·7; H, 4·5%).

2-Amino-4-hydroxy-1 : 3-diaza-acridine (II; R = NH_2, R′ = OH).—A suspension of malonylguanidine (III, R = NH_2) (2 g., 1 mol.) and *o*-aminobenzaldehyde (cf. Bamberger, *Ber.*, 1927, **60**, 319) (3 g., 1·5 mols.) in water (100 c.c.) containing concentrated hydrochloric acid (5 c.c.), was heated on a steam-bath for 1 hour. The precipitated aldehyde polymer was removed and the solution cooled; the aminodiaza-acridine *hydrochloride* (2·7 g., 69·5%) then separated. The salt was quite readily hydrolysed in water and was recrystallised from boiling dilute hydrochloric acid, from which it separated in colourless long needles, m. p. > 310° (Found: C, 46·1; H, 4·3; Cl, 12·3. $C_{11}H_8ON_4,HCl,2H_2O$ requires C, 46·3; H, 4·6; Cl, 12·5%).

The action of sodium carbonate solution on the pure hydrochloride gave the microcrystalline *base* (II; R = NH_2, R′ = OH), m. p. > 310° (Found: C, 62·4; H, 3·6. $C_{11}H_8ON_4$ requires C, 62·2; H, 3·8%). It dissolves in sodium hydroxide to a pale yellow solution with a strong greenish-blue fluorescence.

2 : 4-Dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH).—4-Amino-2 : 6-dihydroxypyrimidine (IV; R = NH_2) (2 g.) and *o*-aminobenzaldehyde (3 g.) were heated in water (100 c.c.) containing concentrated hydrochloric acid (5 c.c.) for an hour. The solid which separated (yield 61%) was collected, washed with alcohol, and purified by precipitation from an alkaline solution with acetic acid. It was very sparingly soluble in water, the alcohols, and acetone, and did not combine with hydrochloric acid. In these properties it was identical with a specimen of 2 : 4-dihydroxy-1 : 3-diaza-acridine (II; R = R′ = OH) prepared from *o*-aminobenzaldehyde and barbituric acid (Conrad and Reinbach, *loc. cit.*) (Found: C, 61·4; H, 3·1; N, 19·3. Calc. for $C_{11}H_7O_2N_3$: C, 62·0; H, 3·3; N, 19·7%).

When the above condensation was repeated in 5% aqueous acetic acid, the compound (II; R = R′ = OH) was once more obtained. On crystallisation from boiling acetic acid the diaza-acridine formed an *acetate*, from which the solvent was expelled on heating to 100° in a vacuum. In this respect it further resembled the authentic diaza-acridine prepared from barbituric acid [Found: C, 57·2; H, 4·1; N, 15·1. $C_{11}H_7O_2N_3,C_2H_4O_2$ requires C, 57·2; H, 4·0; N, 15·4%. Found, after drying at 100°: C, 61·5; H, 3·6; loss 18·9. Found, with authentic specimen of (II; R = R′ = OH): loss, 22·4. $C_{11}H_7O_2N_3$ requires loss, 22·0%].

4-Amino-2-keto-3 : 12-diaza-2 : 12-dihydroacridine (XII).—2 : 4-Diamino-6-hydroxypyrimidine (3 g., 1 mol.) dissolved in water (100 c.c.) containing acetic acid (10 c.c.) was treated with *o*-aminobenzaldehyde (3 g., 1 mol.) in ethanol (10 c.c.). The solution was heated to boiling, and after 1 minute a dense yellow solid began to deposit. In 30 minutes the mixture was cooled, and the product (1·8 g., 35%) collected and crystallised from a large volume of acetic acid. The *diaza-acridine* (XII) was thus obtained as a very sparingly soluble bright yellow microcrystalline powder, m. p. > 330°, giving a

difficultly soluble sodium salt (Found: C, 59·9; H, 4·1; N, 25·4. $C_{11}H_8ON_4,\frac{1}{2}H_2O$ requires C, 59·7; H, 4·1; N, 25·4%). Solutions of the diaza-acridine exhibited a vivid blue fluorescence. The *hydrochloride* crystallised from dilute hydrochloric acid, in which it is very slightly soluble, in minute biscuit-coloured hexagonal plates, m. p. > 310° (Found: C, 53·0; H, 3·7; Cl, 14·5. $C_{11}H_8ON_4,HCl$ requires C, 53·1; H, 3·6; Cl, 14·3%).

2-*Methylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II, R = NHMe, R′ = OH).—A solution of 2-methylamino-4 : 6-dihydroxypyrimidine (1·4 g.) and *o*-aminobenzaldehyde (1·8 g.) in acetic acid (5 c.c.) and water (75 c.c.) was heated under reflux for 30 minutes. After the green aldehyde polymer had been removed by ether, the solution was neutralised with sodium bicarbonate, and the precipitated 2-*methylamino*-4-*hydroxydiaza-acridine* (1·4 g., 63·5%) obtained as stout pale yellow prisms, m. p. > 310° (Found: C, 57·6; H, 5·0. $C_{12}H_{10}ON_4,1\frac{1}{2}H_2O$ requires C, 57·6; H, 5·0%. Found, after drying at 100°: C, 63·5; H, 4·7. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·4%). The diaza-acridine dissolves sparingly in organic solvents, easily in aqueous acids and alkali, and its solutions exhibit a marked green-blue fluorescence.

When the isomeric 4-methylaminodihydroxypyrimidine was similarly treated with *o*-aminobenzaldehyde, the product, recrystallised from acetic acid, was identified as the diaza-acridine (II; R = R′ = OH) (Found: C, 56·7; H, 4·2. Calc. for $C_{11}H_7O_2N_3,C_2H_4O_2$: C, 57·2; H, 4·0%).

4-*Guanidino*-2-*hydroxy*-1 : 3-*diaza-acridine* [II; R = NH·C(:NH)·NH$_2$, R′ = OH].—4-Guanidino-2 : 6-dihydroxypyrimidine (0·5 g.) and *o*-aminobenzaldehyde (0·5 g.) were heated in boiling 25% acetic acid (40 c.c.) for 30 minutes. On cooling, the diaza-acridine [II; R = NH·C(:NH)·NH$_2$, R′ = OH] separated as felted needles (0·6 g., 81%), m. p. > 310°, soluble in aqueous acid and alkali. The base was difficult to purify, but the *dihydrochloride*, m. p. > 310°, was readily crystallised from dilute hydrochloric acid, forming small cream coloured plates, and losing a molecule of hydrogen chloride on drying at 120° (Found: C, 40·3; H, 4·3; Cl, 19·4. $C_{12}H_{10}ON_4,2HCl,1\frac{1}{2}H_2O$ requires C, 40·7; H, 4·2; Cl, 20·0%. Found, after drying: C, 47·0; H, 4·2; loss, 12·2. $C_{12}H_{10}ON_4,HCl,H_2O$ requires C, 46·6; H, 4·2; loss, 12·5%). The compound was further characterised by the *picrate*, which separated from acetic acid in microscopic yellow tablets, m. p. 230° (decomp.) (Found: C, 42·4; H, 3·2. $C_{12}H_{10}ON_4,C_6H_3O_7N_3,1\frac{1}{2}H_2O$ requires C, 42·4; H, 3·2%. Found, after drying at 100°: C, 43·3; H, 3·0; loss, 3·1. $C_{12}H_{10}ON_4,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires C, 43·8; H, 2·8; loss, 3·5%).

2-*γ*-*Diethylaminopropylamino*-4-*hydroxy*-1 : 3-*diaza-acridine* (II; R = NH·[CH$_2$]$_3$·NEt$_2$, R′ = OH).—2-*γ*-Diethylaminopropylamino-4 : 6-dihydroxypyrimidine (7·2 g.) and *o*-aminobenzaldehyde (5·4 g.) were heated to 100° in N-hydrochloric acid (100 c.c.) for 1 hour. The cooled, filtered solution was neutralised with sodium carbonate, and after 12 hours a small amount of flocculent precipitate was removed and the filtrate evaporated under reduced pressure. From the residue the crude diaza-acridine was removed as a reddish oil (7·1 g.) by extraction with absolute alcohol (100 c.c.). The only satisfactory derivative was the *meconate*, which separated as a highly crystalline pale yellow powder on adding excess alcoholic meconic acid. It had m. p. 180° (efferv.) not raised by crystallisation from aqueous ethanol, and was sparingly soluble in the alcohols and acetone, very soluble in water. From 15 c.c. of the alcoholic extract the amount of pure salt was 1·4 g., corresponding to a total yield of 4·9 g. (50·0%) of pure base (Found: C, 48·4; H, 5·7; N, 10·9. $C_{18}H_{23}ON_5,C_7H_4O_7,5H_2O$ requires C, 48·8; H, 6·0; N, 11·4%. Found, after drying at 100°: C, 53·0; H, 5·6; loss, 7·7. $C_{18}H_{23}ON_5,C_7H_4O_7,2\frac{1}{2}H_2O$ requires C, 52·7; H, 5·8; loss, 7·3%). The *picrate*, prepared from the base in ethanol, on boiling with a little acetone was obtained as an alcoholate, a microcrystalline powder, m. p. 222° (decomp.), not capable of further purification (Found: C, 51·7; H, 5·2; N, 18·5. $C_{18}H_{23}ON_5,C_6H_3O_7N_3,C_3H_6O$ requires C, 52·0; H, 5·3; N, 18·7%).

5-(2 : 4-*Dinitrobenzylidene*)*barbituric Acid*.—Barbituric acid (3·9 g., 1·5 mol.) was added to a suspension of 2 : 4-dinitrobenzaldehyde (3·9 g., 1 mol.) in boiling water (150 c.c.); in a few seconds a voluminous pale yellow precipitate of the *dinitrobenzylidene* compound (4·1 g., 71·5%) separated. It was very sparingly soluble in water and ethanol, and gave with sodium hydroxide solution a difficultly soluble sodium salt. The dinitrobenzylidene acid was recrystallised from much acetic acid, giving orange needles, m. p. > 310° (Found: C, 43·6; H, 2·3. $C_{11}H_6O_7N_4$ requires C, 43·1; H, 2·0%).

8-*Nitro*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*.—4-Nitro-2-aminobenzaldehyde (3·5 g., 1 mol.) in warm ethanol (75 c.c.) was added to a solution of barbituric acid (3·5 g., 1·3 mols.) in boiling water (250 c.c.); a copious precipitate rapidly appeared, and after 1 hour the *diaza-acridine* (3·5 g., 64·5%) was collected. It was very slightly soluble in the usual solvents, and was purified by crystallisation from a large volume of acetic acid as cream-coloured fluffy needles, m. p. > 310°, giving a sparingly soluble orange sodium salt (Found: C, 49·0; H, 3·0; N, 17·2. $C_{11}H_6O_4N_4,C_2H_4O_2$ requires C, 49·0; H, 3·1; N, 17·5%). In acetic acid the compound showed the blue fluorescence characteristic of the diaza-acridine nucleus.

The authors thank the Medical Research Council for a maintenance grant to one of them (T. J. K.), and Messrs. Imperial Chemical Industries Ltd., Blackley, Manchester, for gifts of chemicals.

Dyson Perrins Laboratory, Oxford. [*Received, September 13th*, 1946.]

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137. *The Deamination of* 2 : 6-*Dichloro-4-nitroaniline.*

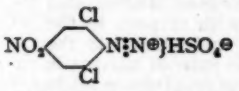
By Dudley Ridge.

The treatment of diazotised 2 : 6-dichloro-4-nitroaniline with ethyl alcohol results in the formation of either 3 : 5-dichloro-1-nitrobenzene or 2 : 2′ : 6 : 6′-tetrachloro-4 : 4′-dinitrodiphenyl according to the conditions of the experiment. The critical factor appears to be the polarity of the nuclear carbon atom to which the diazonium group is attached, and the optimum

experimental conditions for hydrocarbon formation are found to be in harmony with the theoretical considerations.

REMOVAL of the amino-group from 2 : 6-dichloro-4-nitroaniline has been described by Beilstein and Kurbatow (*Annalen*, 1879, **196**, 228), Holleman and Reiding (*Rec. Trav. chim.*, 1904, **23**, 366), and Holleman and de Mooy (*ibid.*, 1915, **35**, 8), the last workers recording a 73% yield of 3 : 5-dichloro-1-nitrobenzene; it has not been possible to repeat this result. Yields were erratic, but usually about 10% of the theoretical quantity of 3 : 5-dichloro-1-nitrobenzene was obtained together with 2 : 2′ : 6 : 6′-*tetrachloro*-4 : 4′-*dinitrodiphenyl*. The best yields of 3 : 5-dichloro-1-nitrobenzene were obtained when the following conditions were observed: (*a*) low temperature; (*b*) slow rate of diazotisation; (*c*) the presence of a little water.

To explain these results it will be seen that in 2 : 6-dichloro-4-nitrobenzenediazonium sulphate both the inductive (— *I*) and mesomeric (— *M*) effects of the nitro-group produce positivity at the carbon atom to which the diazonium radical is attached. The inductive effect (— *I*) of the chlorine atoms operating from the two ortho-positions produce positivity but, on the other hand, the mesomeric effect (+ *M*) will tend to reverse the polarity of the nuclear carbon atom. The combined effect of these substituents is to produce an intermediate state of positivity whereby both diaryl and hydrocarbon formation are possible (cf. Hodgson, Leigh, and Turner, *J.*, 1942, 744). Moreover, this state seems to be critical, since small changes in the experimental conditions produce considerable variation in the relative proportions of the products.



Waters (*J.*, 1942, 266) has shown that diaryl formation may operate through the un-ionised diazo-compound Ar—N=N—X rather than through the ionised diazonium salt Ar—N≡N$^{\oplus}$}X$^{\ominus}$, and therefore conditions which favour the preservation of the latter structure will increase the yield of hydrocarbon at the expense of that of the diaryl. When deamination is carried out by ethyl alcohol in concentrated sulphuric acid, ionisation is inhibited and diaryl formation predominates. On the introduction of a little water, ionisation takes place and increased hydrocarbon formation results. Furthermore, the stability of the diazonium salt is increased by low temperature and slow rate of diazotisation, thus reducing the likelihood of diaryl formation.

Deamination by Hodgson and Turner's method (*J.*, 1942, 748), although performed in the absence of water, gave excellent yields of hydrocarbon with negligible quantities of diaryl. This suggests either that the diazonium ion is maintained in the presence of glacial acetic acid, or more likely (*vide* Hodgson and Turner, *loc. cit.*) that the cuprous oxide acts catalytically as well as functioning as a reducing agent.

EXPERIMENTAL.

Deamination by Ethyl Alcohol and Sulphuric Acid.—(*a*) Ethyl alcohol (37·5 c.c.), concentrated sulphuric acid (18 c.c.), and dry, powdered 2 : 6-dichloro-4-nitroaniline (10 g.) were mixed in a flask with reflux condenser. Finely powdered sodium nitrite (3·6 g.) was slowly added with agitation and cooling. The mixture was heated on the water-bath for 1 hour, and next day was steam-distilled. The crude 3 : 5-dichloro-1-nitrobenzene had m. p. 60° (4·5 g., 41%). Recrystallisation from 50% alcohol raised the m. p. to 65—66° (lit. 65°) (yield 4·0 g., 46%).

(*b*) Ethyl alcohol (75 c.c.), concentrated sulphuric acid (36 c.c.), and 2 : 6-dichloro-4-nitroaniline (21 g.) were treated with sodium nitrite (7·2 g.). The mixture was mechanically stirred but no special precautions were taken to keep the temperature low. No 3 : 5-dichloro-1-nitrobenzene was obtained, but distilllation with superheated steam gave a yellow substance, difficult to purify, m. p. 148—158°. This, recrystallised from boiling trichloroethylene, yielded 2 : 2′ : 6 : 6′-*tetrachloro*-4 : 4′-*dinitrodiphenyl* as a yellow amorphous power, m. p. 184° with a tendency to sublime and decompose [Found: N, 7·20; Cl, 37·40; *M* (Rast), 382. $C_{12}H_4O_4N_2Cl_4$ requires N, 7·33; Cl, 37·17%; *M*, 378].

Similar experiments produced 3 : 5-dichloro-1-nitrobenzene in yields of 14 and 23%.

(*c*) 2 : 6-Dichloro-4-nitroaniline (53 g.) was dissolved in warm concentrated sulphuric acid (93 c.c.). Ethyl alcohol (190 c.c.) was slowly added with cooling, causing the precipitation of the sulphate of the base in a finely divided state. Additional ethyl alcohol (40 c.c.) was added to render the mixture more fluid. The flask was cooled in ice–water and sodium nitrite (38 g. in saturated aqueous solution) added very slowly over a period of 2½ hours, with mechanical stirring. After 1 hour on the water-bath at 100° the mixture was steam-distilled. Yield of recrystallised 3 : 5-dichloro-1-nitrobenzene, 30 g. (61%); m. p. 63—64° (lit. 65°).

Deamination by Hodgson and Turner's Method (loc. cit.).—2 : 6-Dichloro-4-nitroaniline (2 g.) was dissolved in hot glacial acetic acid and rapidly cooled to room temperature. Finely powdered sodium nitrite (0·9 g.) was gradually added to ice-cold concentrated sulphuric acid (7 c.c.) with vigorous stirring, and the mixture then heated on the water-bath to complete solution. The acetic acid solution of the amine was slowly added to the nitrosylsulphuric acid cooled in ice and mechanically stirred. The diazotised mixture was gradually run into a suspension of finely pulverised cuprous oxide (2·8 g.) in ethyl alcohol (25 c.c.), with constant stirring. After being stirred for thirty minutes, the reaction mixture was diluted with an equal volume of water and distilled to remove ethyl alcohol and ethyl

acetate. Steam distillation of the residue gave 3 : 5-dichloro-1-nitrobenzene (1·12 g., 60%); m. p. after recrystallisation from alcohol, 65° (lit. 65°).

The author wishes to express his thanks to I.C.I. Ltd. (Dyestuffs Group) for gifts of chemicals and for permission to publish this work.

DEPARTMENT OF CHEMISTRY AND BIOLOGY,
THE POLYTECHNIC, REGENT STREET, W.1.

[*Received, August 26th*, 1946.]

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138. *The Kinetics of the Reaction between Tin and Solutions of Bromine and Iodine in Organic Solvents.*

By A. F. TROTMAN-DICKENSON and E. J. F. JAMES.

The reaction between tin and halogen (iodine and bromine) solutions has been studied, and the following points established: (1) The reaction is of the first order with respect to the halogen. (2) The velocity constant is proportional to the fluidity of the solvent and to the absolute temperature. (3) The variation of the velocity constant with the rate of stirring is given by the expression $k = Bs + k_0$, where B is a constant, s is the number of revolutions made by the stirrer per minute, and k_0 is the velocity constant when there is no stirring. These results may be explained on the basis of the diffusion theory (Moelwyn-Hughes, "Kinetics of Reaction in Solution", Chapter IX, Oxford Univ. Press, 1933).

THE data relating to the rate of dissolution of solids in solutions of acids and of halogens are meagre. In general, it is found that the kinetics are not governed by chemical considerations at all, but by a diffusion process, though several cases which are exceptions to the diffusion theory have been studied. Usually the chemical reaction taking place at the solid surface is relatively fast. The most comprehensive investigation designed to test the diffusion theory was carried out by Van Name and his co-workers (references in *Amer. J. Sci.*, 1917, **43**, 449); he is the principal worker in this field. Out of a dozen different metals used, it was found that two—magnesium and tin—dissolved faster than would be expected on the basis of the diffusion theory, and this clearly demanded a special explanation. The explanation offered in the case of magnesium is the stirring by hydrogen evolution, and in the case of tin, the fact that this metal can be converted into stannic halide in two stages, so that less halogen need diffuse right to the surface of the tin. Van Name used solutions of iodine in mixtures of iodides and water. Many organic solvents offer the advantage that the iodine is present in the form of simple unsolvated molecules; moreover, the viscosity can be varied over a wide range by the choice of suitable solvent, and hydrogen evolution and salt effects are avoided.

Numerous workers (Wildermann, *Z. physikal. Chem.*, 1909, **66**, 445; Brunner, *ibid.*, 1904, **47**, 56; Friend, *J.*, 1922, 41; Van Name, *loc. cit.*) have made determinations of the effect of the rate of stirring upon the kinetics of reactions governed by a diffusion process. Unless the reacting substance is attached to the blades of the stirrer or is itself the stirrer there is no reason why the stirring effect should be proportional to the rate of revolution of the stirrer. It has been found that when the reacting substance is rotated with the stirrer, a direct proportionality is observed, but when it is suspended in a stirred liquid, the velocity constant varies with the rate of revolution of the stirrer according to some fractional power slightly less than unity. Probably the latter workers just obtained constants for their own apparatus without general significance. When direct proportionality is not observed it would seem likely that attack is not uniform over the whole surface of the reacting body.

EXPERIMENTAL.

The Order of the Reaction.—By studying the rate of loss of weight of a tin cylinder in solutions of iodine in carbon tetrachloride at room temperature or boiling under a reflux condenser or in a chloroform solution of bromine, it was shown that the reaction was of the first order with respect to the halogen. In this case the tin cylinders, which were smoothed with a fine emery paper, were small, of about 0·32 cm. average diameter and 1·5 cm. in length. The readings were obtained by immersing a weighed tin cylinder in the halogen solution for a measured time, after which it is removed, washed in carbon tetrachloride, dried, and re-weighed. The halogen solutions were made up to a suitable initial concentration, a known weight of iodine or known volume of bromine being dissolved in 100 c.c. of solvent.

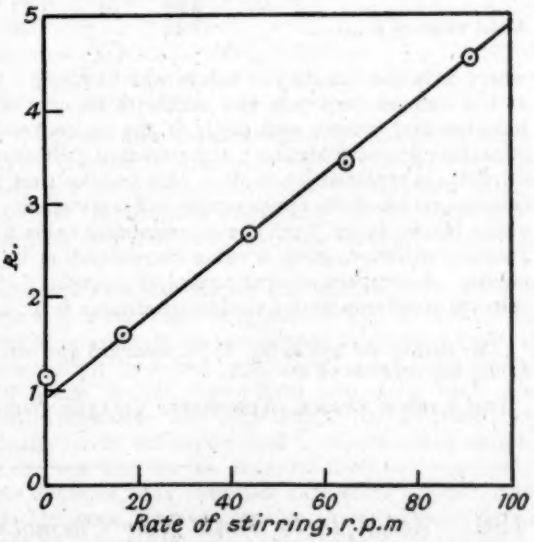
The Effect of the Surface Area of the Cylinder upon the Velocity Constant.—It would be expected, on the basis of most possible theories and certainly on the diffusion theory, that the velocity constant of the first-order reaction would be proportional to the surface area of the tin cylinder. Because of the importance of this for the purpose of correlating results obtained with different cylinders, the proportionality had to be verified. This was done by determining the velocity constant for two cylinders,

one having twice the surface area of the other: the smaller was 1·87 cm. long, and the larger 4·13 cm. long, both being of 0·78 cm. diameter. The procedure was as before; the bromine solution, containing 1·9 c.c. of bromine in 50 c.c. of chloroform, was kept in a stoppered glass bottle in a thermostat maintained at 20° during the experiment. It was found that the velocity constant was proportional to the surface area of the cylinder to within 1%, the ratio of the two constants being 1 : 2·01.

The Effect of the Fluidity of the Solvent upon the Velocity Constant.—For this series of experiments the cylinders were small, 1·44 cm. long and 0·31 cm. in diameter, the weights being the same within 0·003 g.; they were all cut from the same tin rod, and all smoothed with the same grade of emery paper. Their surface areas may therefore be considered identical. The solvents employed were chloroform, carbon tetrachloride, and ethylene dibromide, none of which reacts appreciably with the bromine in the few hours for which the solutions are used, at the temperature of the experiment. The experiment was conducted in stoppered glass bottles in a thermostat at 20°, and the procedure was as before. The results obtained are recorded in Table I. In all cases the velocity constant is multiplied by 100. The values quoted for the fluidities are due to Thorpe and Rodger; time is expressed in minutes throughout. The values for k are obtained by using the formula $k = (1/t) \ln W_1/W_2$, where t is the time between successive weighings, and W_1 and W_2 are the weights of the tin cylinder before and after immersion. The result of this experiment shows that the velocity constant is directly proportional to the fluidity of the solvent.

TABLE I.

	Chloroform.		Carbon tetrachloride.		Ethylene dibromide.	
	Time.	k.	Time.	k.	Time.	k.
	80	0·124	80	0·073	80	0·043
	180	0·124	180	0·073	180	0·041
	280	0·143	320	0·076	320	0·039
	450	0·108	450	0·074	450	0·041
Mean value of k		0·124		0·074		0·041
Fluidity of solvent, $1/\eta$		177		104		58·3
$k\eta \times 10^4$		0·702		0·711		0·703



The Effect of the Temperature upon the Velocity Constant.—From the foregoing, it follows that if the temperature effect is to be investigated, allowance must be made for the variation of the fluidity with temperature. In this experiment, the tin cylinders employed were of the larger diameter and had surface areas varying between 5·5 and 6 sq. cm. Accordingly, all the velocity constants are here reduced to unit surface area. The solutions used were all of chloroform containing 20 c.c. of bromine per l. The results obtained are given in Table II: again, k is multiplied by 100, but $k\eta$ by 10^5. The product $k\eta$ divided by the absolute temperature is found to be constant, so k is directly proportional to the absolute temperature.

The Effect of the Rate of Stirring on the Velocity Constant.—To investigate the effect of altering the rate of stirring upon the velocity constant the tin cylinder was itself rotated: this is the best way to ensure that the stirring effect at the surface of the cylinder is proportional to the rate of revolution of the latter. The tin cylinder used had a short glass rod fitted into a hole bored through the radial axis; the rod was attached by a screw connector to the driving shaft of the stirrer. The rate of stirring was measured by counting the number of revolutions in 0·5 minute at convenient intervals. The bromine solution used contained 1 c.c. of bromine in 50 c.c. of chloroform and was kept at 20° in a thermostat. The results obtained are given in Table III, and are summarised in the figure, from which it will be seen that the variation of the velocity constant with the rate of stirring is given by the equation $k = Bs + k_0$.

Discussion.—The results obtained in the above experiments may be summarised in the equation $dw/dt = ZATw/\eta$, where w is the concentration of the halogen solution, dw/dt is the rate of reduction of its concentration, A the surface area of the cylinder, T the absolute temperature, η the viscosity of the solution, and Z is a constant. This may be compared with the equation obtained on the basis of the diffusion theory; it is a combination of Fick's law and the Stokes–Einstein diffusion law:

$$\frac{ds}{dt} = A \frac{dc}{dx} \frac{RT}{N} \frac{1}{6\pi\eta r}$$

TABLE II.

Temperature:	20°.		25°.		35°.		40°.	
	Time.	k.	Time.	k.	Time.	k.	Time.	k.
	10	0·0920	10	0·0965	10	0·1267	10	0·1588
	20	0·1081	20	0·1318	20	0·1773	20	0·1266
	30	0·1069	30	0·1312	30	0·1196	30	0·1312
	40	0·1382	40	0·1150	40	0·1082	40	0·1472
	50	0·0965	50	0·0903	50	0·1312	50	0·1289
			60	0·0903	60	0·1289	60	0·1610
			70	0·1358	70	0·1289	70	0·1266
			80	0·1266				
Mean value of k		0·1082		0·1150		0·1312		0·1404
Viscosity of $CHCl_3$		0·00564		0·00537		0·00485		0·00460
$k\eta \times 10^3$		0·7855		0·7907		0·0836		0·8111
Temp., °K.		293		298		308		313
$10^5 k\eta/T$		0·207		0·208		0·206		0·206

TABLE III.

Rate of stirring, r.p.m.:	0.		17.		44.		65.		92.	
	Time.	k.	Time.	k.	Time.	k.	Time.	k.	Time.	k.
	10	1·12	10	1·49	2·25	2·30	10	3·56	5	5·12
	20	1·07	20	1·57	17·75	2·58	20	3·51	10	4·39
	30	1·05	30	1·61	27·75	2·95	30	3·18	15	4·16
	40	1·37	41	1·57	39	2·78	40	3·57	22	5·22
	50	0·95	51	1·77	49	2·76			30	3·82
Mean value of k		1·12		1·60		2·67		3·46		4·58

where ds is the quantity of solute which crosses a boundary of area A in time dt, r is the radius of the halogen molecule and accounts for the difference in rates of reaction in the cases of bromine and iodine, and dc/dz is the concentration gradient. It will be seen that the two equations are very similar; the principal difference is that w, the concentration of the halogen solution, is replaced by dc/dz. This implies that the Nernst layer is of constant thickness and is independent of the temperature and the viscosity of the solution. Calculation of the thickness of the Nernst layer, from the experimental value for the velocity constant and the Fick–Stokes–Einstein equation, gives a value corresponding to about 10,000 molecular diameters of stannic iodide. A comparison of the rates of reaction of iodine and bromine shows that the ratio of the velocity constants under similar conditions is 3 : 4.

Our thanks are due to Mr. F. W. Goddard and Mr. R. P. Bell, F.R.S., for help and encouragement during the progress of the work.

THE SCIENCE SCHOOL, WINCHESTER COLLEGE, WINCHESTER. [*Received, September 6th*, 1946.]

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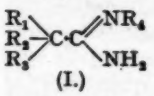
139. *Attempts to Find New Chemotherapeutic Amidines. Part VIII. Some Aliphatic Monoamidines.*

By G. NEWBERY and W. WEBSTER.

A number of aliphatic monoamidines of varying molecular weight and structure have been prepared for testing as bactericides against *M. tuberculosum*. Most of these were obtained by the sodamide method from the corresponding cyanides, which in turn were made mainly by the sodamide method of alkylation of aliphatic cyanides. Some of the limitations of these methods are discussed.

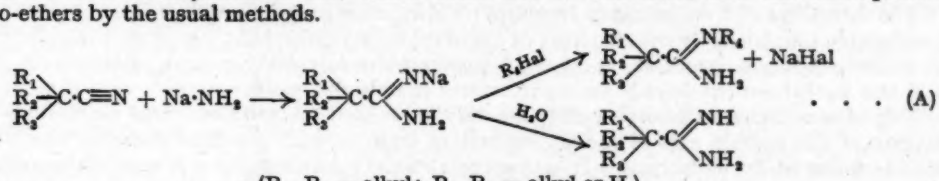
ADAMS, STANLEY, and their co-workers (*J. Pharm. Exp. Ther.*, 1932, **45**, 121) have shown that certain dialkylacetic acids possess appreciable bactericidal activity against *M. lepræ* (at that time thought to be the infective agent causative of leprosy). This activity is most marked with acids which contain 16 to 18 carbon atoms, particularly when the carboxyl group is situated at or near the centre of the molecule, and does not appear to be confined to the carboxylic acids, as similar compounds containing the grouping $CH_2{\cdot}NEt_2$ in place of the carboxyl group are only slightly less active. These authors also found that some of these acids are active against the

closely related organism *M. tuberculosum*. The preparation of a series of aliphatic monoamidines for testing as possible tuberculocidal agents is described in the present work. These have the general formula (I), where R_1 = alkyl and R_2, R_3, R_4 = alkyl or H, and include compounds varying in molecular weight from amidines containing 7 to 18 carbon atoms, and in molucular structure from unsubstituted simple straight-chain amidines (I; R_1 = *n*-alkyl, $R_2 = R_3 = R_4$ = H) to *N*-alkyl trialkylacetamidines (I; R_1, R_2, R_3, R_4 = alkyl).



(I.)

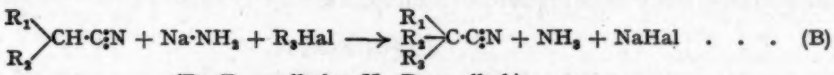
With the exception of stearamidine (Pinner, " Die Imido Äther ", p. 130), all these compounds were prepared from the corresponding cyanides by Ziegler's sodamide method (U.S.P., 2,049,582) as represented in scheme (A). This method proved particularly successful in the case of the higher di- and tri-alkylacetonitriles, which could not be converted into the corresponding imino-ethers by the usual methods.



. . . (A)

(R_1, R_4 = alkyl; R_2, R_3 = alkyl or H.)

Most of the cyanides were also prepared by the sodamide method of alkylating aliphatic cyanides as described by Ziegler and Ohlinger (*Annalen*, 1932, **495**, 84) and represented in scheme (B). It provided a particularly convenient route to the higher molecular weight trialkylacetonitriles whose synthesis by other methods would have proved difficult and tedious.



. . . (B)

(R_1, R_2 = alkyl or H; R_3 = alkyl.)

Ziegler and Ohlinger (*loc. cit.*) showed that in most cases the alkylation process (B) is much more rapid than is amidine formation (A), and on the basis of this observation devised methods whereby, from the reaction between a cyanide and sodamide there could be obtained nearly theoretical yields of amidine or alkylated cyanide respectively depending on the absence or presence of alkyl halide. In one or two cases lower yields resulted with sterically hindered molecules.

In the present work the influence of the steric structure was particularly noticeable in amidine formation. For instance, reaction of sodamide with α-ethyl-α-*n*-butylacetonitrile occurred with evolution of heat and was complete in a matter of minutes, giving an almost theoretical yield of *α-ethyl*-α-n-*butylacetamidine*, while the corresponding reaction with *α-ethyl*-α-n-*butyl*-α-sec.-*octylacetonitrile*, required heating for 48—72 hours on the steam-bath and even then the maximum yield of *α-ethyl*-α-n-*butyl*-α-sec.-*octylacetamidine* was only 32%. In contrast, the monoalkyl-acetonitriles reacted almost violently with sodamide and in these cases simple amidine formation did not appear to be the sole reaction as the expected amidines were only isolated in very poor yield. *Decoamidine*, for example, was obtained only in 10% yield, and no stearamidine was obtained by this method. Moreover, no *N*-*n*-octyldecoamidine was isolated after treating the reaction product of sodamide and deconitrile with *n*-octyl bromide. However, these results are inconclusive, as these particular compounds can only be isolated from the reaction mixture as crystalline salts, *e.g.*, hydrochlorides, and it is difficult to crystallise long-chain aliphatic compounds of this type in the presence of any appreciable amounts of by-products. In general, it seems that simple straight-chain aliphatic amidines are obtained more satisfactorily by the imino-ether than by the sodamide method.

The dependence of the rate of reaction on the steric configuration is less marked in alkylation reactions. For instance, di- and tri-alkylation of acetonitrile can be effected in one stage, but at the same time there is sufficient difference in the rates of alkylation of unsubstituted and substituted acetonitriles to allow the preparation of any desired product in satisfactory yield. In a typical experiment the monoalkylation of acetonitrile with *n*-octyl bromide and sodamide gave deconitrile in 52% yield together with a 10% yield of *di*-n-*octylacetonitrile*. Similarly *di*-n-*hexylacetonitrile* was formed in about 10% yield during monoalkylation of acetonitrile, in 42% yield by dialkylation of acetonitrile, and in 45% yield by the partial alkylation of octonitrile.

Of more significance in alkylation is the varying reactivity of the halogen atom of the alkyl halide according to the nature of the alkyl groups involved. Ziegler and Ohlinger (*loc. cit.*)

instance the difficulty of introducing the *cyclo*hexyl group, and in the present work similar trouble was experienced in alkylation with *sec.*-octyl bromide. The alkylation of ethylbutylacetonitrile with *n*-octyl bromide gives *α-ethyl-α-butyl-α-n-octylacetonitrile* in 80% yield, while with *sec.*-octyl bromide the yield of α-ethyl-α-*n*-butyl-α-*sec.*-octylacetonitrile was only 33%. Moreover, the latter nitrile was accompanied by appreciable quantities of *α-ethyl-α-n-butylacet-N'-sec.-octylamidine hydrobromide*, indicating that the rate of alkylation with the less reactive *sec.*-octyl bromide is of the same order as that of amidine formation. Again, in the attempted alkylation of acetonitrile with *sec.*-octyl bromide, only traces of material corresponding to the mono- and di-*sec.*-octylacetonitriles were obtained. In this case polymerisation of the acetonitrile seemed to take place much more rapidly than did alkylation and diacetonitrile was the main reaction product.

The formation of *N*-substituted amidines by alkylation of sodio-amidines also appears to be considerably influenced by the structure of the alkyl halide employed; *e.g.*, from the sodium salt of *α-ethyl-α-n-butylacetamidine*, *α-ethyl-α-n-butylacet-N-n-octylamidine* was obtained in 40% yield but *α-ethyl-α-n-butylacet-N-sec.-octylamidine* in only 8% yield.

N-(p-Aminobenzenesulphonyl)-α-ethyl-α-n-butyl-α-sec.-octylacetamidine was obtained by reaction of the sodium salt of the corresponding amidine with *p*-acetamidobenzenesulphonyl chloride followed by hydrolysis. It was soluble in the usual organic solvents but completely insoluble in water and, similarly to other sulphanilylamidines (cf. Northey, Pierce, and Kertesz, *J. Amer. Chem. Soc.*, 1942, **64**, 2763), it was also insoluble in alkali.

Biological data on these compounds will be published elsewhere, but preliminary investigation indicated that, while some of these amidines possess bactericidal properties and show marked *in vitro* activity against *M. tuberculosum*, they were considered too toxic for the prolonged administration likely to be required to demonstrate activity against guinea pig infections.

Experimental.

Suspensions of sodamide in benzene were prepared and estimated as described by Ziegler and Ohlinger (*loc. cit.*, p. 106).

Ethyl-*n*-butylacetonitrile and ethyl*iso*propylacetonitrile were prepared from the corresponding malonic ester and acetic acids respectively by the usual methods.

Alkylation of Nitriles with Sodamide and Alkyl Halide.—The apparatus consisted of a 3-necked flask carrying a sealed stirrer, a condenser, and a dropping funnel, which was fitted with a small stirrer. The nitrile (1 mol.) and alkyl halide (1 mol.) were placed in the flask with an equal volume of dry benzene and heated on the steam-bath, to 45° for the monoalkylation of acetonitrile, and to 80° for alkylation of substituted acetonitriles. The suspension of sodamide (1 mol.), mechanically stirred to ensure homogeneity, was introduced from the dropping funnel, under stirring, at such a rate that fairly brisk but not violent reaction was maintained, or in the case of monoalkylation of acetonitrile, that the temperature did not rise above 50°. When addition of sodamide was complete, heating was continued for about one hour to complete the reaction. When the mixture was cool, water was carefully added to it and the benzene layer was separated, washed with water, and dried over sodium sulphate. The benzene was removed, and the product distilled under reduced pressure, with redistillation through a column when necessary. Where dialkylation of acetonitrile was attempted the procedure was essentially the same. Two mols. of alkyl halide and sodamide were used to one of acetonitrile; the temperature was kept below 50° until one mol. of sodamide had been added, and then allowed to rise to the boiling point of benzene while the second mol. was introduced.

Amidine Formation.—A stirred sodamide suspension (1·1 mols.) was slowly added with stirring to a solution of the nitrile (1 mol.) in benzene (an equal volume in the case of the lower aliphatic nitriles and about half the volume with the higher members of the series). With nitriles of comparatively low molecular weight a fairly brisk reaction usually occurred after a few minutes, and in some cases cooling in ice was necessary to moderate this reaction. When all the sodamide was added the mixture was heated for some time on the steam-bath to complete the reaction. With the higher secondary and tertiary acetonitriles, however, no reaction occurred during the sodamide addition and the mixture had to be heated on the steam-bath with stirring for periods up to 73 hours. When reaction was complete, the product was in the form of a crystalline mass of the sodio-amidine. Water was added carefully with ice cooling until two clear layers were obtained; the benzene layer was washed with a small amount of water and dried over sodium carbonate. The subsequent isolation and purification of the product varied according to the particular properties of the amidine concerned. In some cases repeated fractionation under reduced pressure yielded a pure compound; in others the hydrochloride was purified by recrystallisation from acetone or alcohol–acetone. Generally, where it was possible, a combination of these two procedures was more satisfactory.

N-Substituted amidines were obtained by addition of an alkyl bromide (1 mol.) to the sodio-amidine obtained as above and refluxing on the steam-bath for about 6 hours, or until the separation of sodium halide was complete. The mixture was then diluted with water, and the amidine worked up as in the case of the unsubstituted derivatives. It was sometimes advantageous to isolate and purify the unsubstituted amidine, dissolve it in benzene, and convert it into the sodio-amidine by addition of the theoretical quantity of sodamide and then treat this with the alkyl bromide. The product obtained by this method was usually more readily purified.

The amidine bases were obtained as colourless viscous oils or crystalline solids of low m. p., which

tended to lose their crystalline form on standing in the atmosphere. They were all soluble in the usual organic solvents but could generally be crystallised from light petroleum (b. p. 40—60°) by cooling a solution to low temperatures. The lower members were soluble in water, but solubility decreased rapidly with increase of molecular weight, and this was also the case with their hydrochlorides. The hydrochloride of an amidine containing 16 carbon atoms was soluble only in 500 parts of water. In the hope of finding a more soluble salt suitable for biological testing, the nitrate, sulphate, isethionate, tartrate, citrate, and gluconate of stearamidine were prepared, but none was soluble in 1000 parts of water. On the other hand, the hydrochlorides were quite soluble in methyl and ethyl alcohol.

The stability of the amidine group in these compounds depends as might be expected on their structure, the order of stability of the acetamidines being tertiary > secondary > primary. In general, it was observed that (i) primary acetamidines decomposed on attempted distillation under pressures of the order of 1 mm., while secondary and tertiary amidines were stable under these conditions, and (ii) primary and secondary acetamidines were readily hydrolysed by alkali to the corresponding amides, while the tertiary amidines were remarkably stable to hydrolytic agents. For instance α-ethyl-α-*n*-butyl-α-*sec.*-octylacetamidine was recovered unchanged after boiling for 24 hours with 50% alcoholic potassium hydroxide, and similarly was not affected by the action of nitrous acid in sulphuric acid.

The nitriles were all obtained as colourless oils. They were stable at the temperatures required for their distillation under reduced pressure but their susceptibility to hydrolysis appeared to be of the same order as that of the corresponding amidines.

The following nitriles and amidines were prepared by these methods: Deconitrile, from *n*-octyl bromide, sodamide, and acetonitrile in 52% yield, b. p. 120°/19 mm., $n_D^{18°}$ 1·4310 (Found: N, 9·05. Calc. for $C_{10}H_{19}N$: N, 9·15%); *di*-n-*octylacetonitrile* was obtained in the preceding experiment in approx. 10% yield, b. p. 196—197°/10 mm., $n_D^{18°}$ 1·4468 (Found: N, 5·3. $C_{18}H_{35}N$ requires N, 5·3%); octonitrile, from *n*-hexyl bromide, sodamide, and acetonitrile in 59% yield, b. p. 111°/37 mm., $n_D^{18°}$ 1·4240 (Found: N, 11·1. Calc. for $C_8H_{15}N$: N, 11·2%); *di*-n-*hexylacetonitrile* was formed in about 10% yield in the preceeding experiment, in about 45% yield from octonitrile, sodamide, and hexyl bromide, and in 42% yield by dialkylation of acetonitrile, b. p. 154°/17 mm., $n_D^{23°}$ 1·4411 (Found: N, 6·5. $C_{14}H_{27}N$ requires N, 6·7%); α*α-diethyl*-α-n-*butylacetonitrile*, from diethylacetonitrile, sodamide, and butyl bromide in 65% yield, b. p. 92°/14 mm. (Found: N, 9·0. $C_{10}H_{19}N$ requires N, 9·15%); *ethyl*iso*propyl*-n-*hexylacetonitrile*, from ethyl*iso*propylacetonitrile, sodamide, and hexyl bromide in 54% yield, b. p. 135°/22 mm., $n_D^{18°}$ 1·4430 (Found: N, 7·4. $C_{13}H_{25}N$ requires N, 7·2%); *ethyl*-n-*butyl*-n-*hexylacetonitrile*, from ethylbutylacetonitrile, sodamide, and *n*-hexyl bromide in 70% yield, b. p. 151—153°/17 mm., $n_D^{22°}$ 1·4439 (Found: N, 6·75. $C_{14}H_{27}N$ requires N, 6·7%); *ethyl*-n-*butylbenzylacetonitrile*, from ethylbutylacetonitrile, benzyl chloride, and sodamide in 76% yield, b. p. 126°/0·5 mm., $n_D^{23°}$ 1·5030, (Found: N, 6·55. $C_{15}H_{21}N$ requires N, 6·5%); *ethyl*-n-*butyl*-sec.-*octylacetonitrile*, from ethylbutylacetonitrile, *sec.*-octyl bromide, and sodamide in 33% yield, b. p. 138°/1 mm. (Found: N, 6·2. $C_{16}H_{31}N$ requires N, 5·9%); *ethyl*-n-*butyl*-n-*octylacetonitrile*, from ethylbutylacetonitrile, sodamide and *n*-octyl bromide in 80% yield, b. p. 129°/1 mm., $n_D^{17°}$ 1·4469 (Found: N, 5·95. $C_{16}H_{31}N$ requires N, 5·9%); *decoamidine hydrochloride*, from deconitrile and sodamide in about 10% yield, m. p. 116°, hygroscopic (Found: N, 13·65; Cl, 17·25. $C_{10}H_{22}N_2$,HCl requires N, 13·55; Cl, 17·2%) (the free base decomposed on attempted distillation under 1 mm. pressure); α-*ethyl*-α-iso*propylacetamidine* was obtained in about 80% yield as its water-soluble *hydrochloride*, m. p. 208—209° (Found: N, 17·3; Cl, 21·6. $C_7H_{16}N_2$,HCl requires N, 17·0; Cl, 21·6%); the free base, recovered from the hydrochloride had b. p. 74—76°/0·05 mm., $n_D^{18°}$ 1·4768 (Found: N, 21·5. $C_7H_{16}N_2$ requires N, 21·9%); α-*ethyl*-α-n-*butylacetamidine*, yield up to 90%, b. p. 113°/2 mm. (Found: N, 19·4. $C_8H_{18}N_2$ requires N, 19·7%), did not yield a crystalline hydrochloride; *picrate*, m. p. 110° (Found: N, 18·9. $C_8H_{18}N_2,C_6H_3O_7N_3$ requires N, 18·9%); *monobenzoyl* derivative, m. p. 125—127° (Found: N, 11·9. $C_{15}H_{22}ON_2$ requires N, 11·4%); *dibenzoyl* derivative, m. p. 167—168° (Found: N, 7·9. $C_{22}H_{26}O_2N_2$ requires N, 8·0%); α*α-di*-n-*hexylacetamidine*, b. p. 125°/0·08 mm., m. p. 32—34° (Found: N, 12·5. $C_{14}H_{30}N_2$ requires N, 12·4%), the yield was only about 20% pure product because of difficulty in purifying the crude reaction product which contained an appreciable amount of amide; *picrate*, m. p. 85—86° (Found: N, 15·5. $C_{14}H_{30}N_2,C_6H_3O_7N_3$ requires N, 15·4%); αα-di-*n*-octylacetamidine, isolated in about 30% yield as its *hydrochloride*, m. p. 99—100° (Found: N, 9·0. Cl, 11·05. $C_{18}H_{38}N_2$,HCl requires N, 8·8; Cl, 11·1%); the free base recovered from the hydrochloride had m. p. 48—50°; α-*ethyl*-α-n-*butylacet*-N-sec.-*octylamidine hydrochloride*, by alkylation of the sodium salt of ethylbutylacetamidine, m. p. 214—216° (Found: N, 9·6; Cl, 12·2. $C_{16}H_{34}N_2$,HCl requires N, 9·6; Cl, 12·2%); *hydrobromide*, m. p. 180—181° (Found: N, 8·25; Br, 23·9. $C_{16}H_{34}N_2$,HBr requires N, 8·35; Br, 23·8%); α-*ethyl*-α-n-*butylacet*-N-n-*octylamidine*, isolated in about 40% yield of pure base, b. p. 162—165°/1 m., $n_D^{14°}$ 1·4695 (Found: N, 10·7. $C_{16}H_{34}N_2$ requires N, 11·0%), did not form a crystalline hydrochloride; α*α-diethyl*-α-n-*butylacetamidine* distilled between 120° and 130°/2 mm. and recrystallised from light petroleum (b. p. 40—60°), m. p. 56—58° (Found: N, 16·1. $C_{10}H_{22}N_2$ requires N, 16·5%) (yield, *ca.* 80%, did not form a crystalline hydrochloride); *picrate*, m. p. 113—114·5° (Found: N, 17·6. $C_{10}H_{22}N_2,C_6H_3O_7N_3$ requires N, 17·5%); α-*ethyl*-α-iso*propyl*-α-n-*hexylacetamidine*, b. p. 122°/15 mm., $n_D^{18°}$ 1·4822 (Found: N, 13·15. $C_{13}H_{28}N_2$ requires N, 13·2%) (yield, 40%), did not form a crystalline hydrochloride; α-*ethyl*-α-n-*butyl*-α-n-*hexylacetamidine*, b. p. 149°/1 mm., $n_D^{21°}$ 1·4789 (Found: N, 12·1. $C_{14}H_{30}N_2$ requires N, 12·4%) (yield, 75%), did not form a crystalline hydrochloride; α-*benzyl*-α-*ethyl*-α-n-*butylacetamidine*, a glass-like gum, b. p. 178°/1 mm. (Found: N, 11·8. $C_{15}H_{24}N_2$ requires N, 12·1%) (yield, 70%); α-*ethyl*-α-n-*butyl*-α-sec.-*octylacetamidine hydrochloride*, m. p. 146—147° (Found: N, 9·5; Cl, 12·3. $C_{16}H_{34}N_2$,HCl requires N, 9·6; Cl, 12·2%) (yield, 32%); α-*ethyl*-α-n-*butyl*-α-n-*octylacetamidine*, b. p. 165°/0·8 mm., $n_D^{21°}$ 1·4757 (Found: N, 11·0. $C_{16}H_{34}N_2$ requires N, 11·0%) (yield about 50%), did not form a crystalline hydrochloride; α*α-diethyl*-α-n-*butylacet*-N-sec.-*octylamidine*, b. p. 156°/2 mm. (Found: N, 10·1. $C_{18}H_{38}N_2$ requires N, 9·9%), did not form a crystalline hydrochloride or picrate.

Stearamidine was prepared by the method of Pinner (*loc. cit.*), and the hydroochloride obtained as a colourless crystalline product which melted partly at 80° and completely at 236° (lit. m. p. 220°) (Found: N, 8·9; Cl, 11·0. Calc. for $C_{18}H_{38}N_2$,HCl: N, 8·8; Cl, 11·1%). The free base recovered from the

hydrochloride had m. p. 80—83° (Found: N, 9·8. Calc. for $C_{18}H_{32}N_2$: N, 9·9%). The *isethionate*, melted partly at 60° and completely at 195° (Found: N, 6·95. $C_{18}H_{32}N_2,C_2H_4O_4S$ requires N, 6·9%).

N-(p-*Acetamidobenzenesulphonyl*)-α-*ethyl*-α-n-*butyl*-α-sec.-*octylacetamidine*.—To α-ethyl-α-*n*-butyl-α-*sec.*-octylacetamidine (6·4 g.) dissolved in dry ether (10 c.c.) was added gradually and with stirring finely ground sodamide (1 g.) in benzene. The mixture was warmed on the steam-bath for 10 minutes, cooled, and *p*-acetamidobenzenesulphonyl chloride (4·8 g.) added. A smooth reaction took place with separation of sodium chloride. The mixture was heated on the steam-bath for 30 minutes, cooled, treated with water, and the ethereal layer separated. On addition of light petroleum (b. p. 40—60°), the required *sulphonylamidine* separated and was filtered off. It recrystallised from benzene in rhombohedral plates, m. p. 137° (Found: N, 9·5. $C_{34}H_{41}O_3N_3S$ requires N, 9·3%) (yield, 2·8 g.). It was soluble in ethanol, methanol, acetone, and chloroform, insoluble in light petroleum, water, dilute mineral acids, and alkali.

N-(p-*Aminobenzenesulphonyl*)-α-*ethyl*-α-n-*butyl*-α-sec.-*octylacetamidine*.—The above acetyl compound (2·5 g.) was refluxed for 6 hours with 1·5N-aqueous-alcoholic sodium hydroxide (30 c.c.). On cooling, an oil separated which readily crystallised. It was filtered off and recrystallised from aqueous alcohol and from benzene–light petroleum in laminæ; m. p. 74—76° (Found: C, 64·8; H, 10·3; N, 10·6; S, 7·4. $C_{32}H_{39}O_3N_3S$ requires C, 64·5; H, 9·5; N, 10·3; S, 7·8%). It was soluble in ethanol, methanol, acetone, chloroform and benzene, and insoluble in water, dilute acids and alkali.

The above project was an extension of attempts in these laboratories to find new chemotherapeutic amidines, and at the same time part of a scheme of pooled research directed towards the discovery of new tuberculocides under The Therapeutic Research Corporation of Great Britain Ltd., to the Directors of which we express our thanks for permission to publish the above results. Our thanks are also due to Mr. S. Bance, B.Sc., A.R.I.C., who was responsible for the semi-microanalyses recorded.

RESEARCH LABORATORIES, MAY & BAKER LTD., DAGENHAM. [*Received, September 10th*, 1946.]

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140. *Acenaphthene Series. Part II. Bromo-, Nitro-, and Amino-derivatives of* 3 : 4-*Di*-tert.-*butylacenaphthene, and some Brominated Thioindigoid Dyes. Novel* ace*Substitution.*

By ARNOLD T. PETERS.

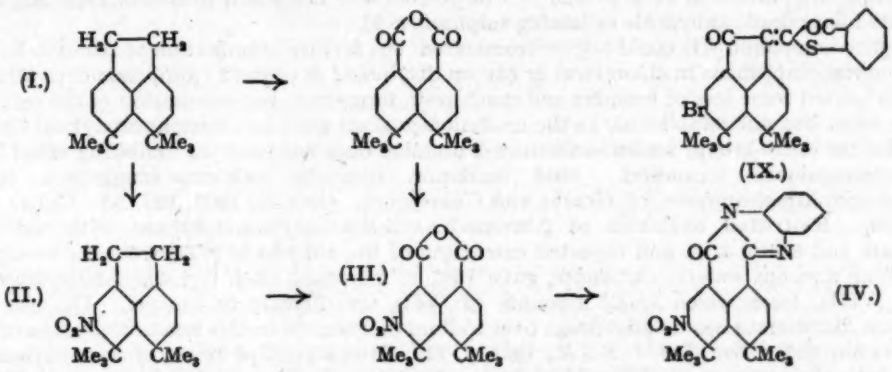
Nitration of 3 : 4-di-*tert.*-butylacenaphthene (I) gives 2-*nitro*- (II) and then 2 : (?)7-*dinitro*-3 : 4-*di*-tert.-*butylacenaphthene* (V), both of which are oxidised to the colourless 3-*nitro*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* (III). No trace of a dinitro-4 : 5-di-*tert.*-butylnaphthalic anhydride is detected by oxidising (V), and the orientation of (III) is supported by its preparation from 4 : 5-di-*tert.*-butylnaphthalic anhydride. Although the presence of the nitro-group in the acenaphthene derivatives inhibits acenaphthenequinone formation, bromine substitution does not. Thus, restricted oxidation of 2-*bromo*-3 : 4-*di*-tert.-*butylacenaphthene* (VI) gives 16% of 2-*bromo*-3 : 4-*di*-tert.-*butylacenaphthenequinone* (VIII), from which the scarlet 2′(or 5′)-*bromo*-3′ : 4′-*di*-tert.-*butyl*-1 : 7′-*thionaphthenacenaphthenylindigo* (IX) and analogous vat *dyes* are prepared. Further oxidation of (VI) or (VIII) yields 3-*bromo*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* (VII), which condenses with *o*-phenylenediamine to give the bright canary-yellow 2′(or 5′)-*bromo*-9′-*keto*-3′ : 4′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 3)-ψ-*indole*.

3-*tert.*-BUTYL- and 3 : 4-di-*tert.*-butyl-acenaphthene (I) were obtained by the direct *tert.*-butylation of acenaphthene, and several new thioindigoid vat dyes were prepared (Part I; *J.*, 1942, 562); the preparation and properties of nitro-, amino-, and bromo-derivatives of (I) are now examined.

With 1·2 mols. of nitric acid (*d* 1·5) or its equivalent of diacetylorthonitric acid, (I) gave 2-*nitro*-3 : 4-*di*-tert.-*butylacenaphthene* (II). On restricted oxidation with sodium dichromate and acetic acid at 105°, under conditions whereby the unnitrated analogue gave 3 : 4-di-*tert.*-butylacenaphthenequinone, (II) gave no quinone, and no product was detected which condensed with 2-hydroxythionaphthen to give a thionaphthenacenaphthenylindigo dye. This is parallel to the case of 3-nitroacenaphthene, from which 3-nitroacenaphthenequinone could not be obtained by a variety of methods of oxidation (cf. Graebe and Briones, *Annalen*, 1903, **327**, 80; Morgan and Harrison, *J. Soc. Chem. Ind.*, 1930, **49**, 413 T). The sole oxidation product of (II) isolated was the colourless 3-*nitro*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* (III), which gave an *imide* and a N-*methylimide*, condensed with *o*-phenylenediamine in acetic acid to yield 2′(or 5′)-*nitro*-9′-*keto*-3′ : 4′-*di*-tert.-*butyl*-8′-*azaphenalino* (7′ : 8′ : 2 : 3)-ψ-*indole* (IV), and showed the expected formation of a naphthafluorescein on fusion with resorcinol, and of a colouring matter of the rhodamine type with *m*-diethylaminophenol.

A chloronaphthafluorescein was prepared from 4-chloronaphthalic anhydride by Dziewoński and Zakrzewskwa-Barnaowska (*Bull. intern. Acad. Polonaise*, 1926, *A*, 209) and Tanaka and Morikawa (*J. Chem. Soc. Japan*, 1930, **51**, 121), and Ferrario and Weber (*Arch. sci. phys. nat.*,

1908, 25, 517) prepared rhodamine derivatives from naphthalic anhydride and *m*-diethyl- and -dimethyl-aminophenol, respectively.



With excess of nitric acid (*d* 1·5) at 95—100°, even in presence of 25% fuming sulphuric acid, 4 : 5-di-*tert.*-butylnaphthalic anhydride could be mononitrated only, and the nitration product was identical with (III). This supports the constitution of (III) and thence of (II), as the dicarboxylic anhydride group directs the nitro-group into the 3-position even when the 4 : 5-positions of naphthalic anhydride are free (cf. Anselm and Zuckmayer, *Ber.*, 1899, **32**, 3283; Graebe and Briones, *loc. cit.*; Mihăilescu and Stoepoe, *Bull. Acad. Sci. Roumaine*, 1923, **8**, 102). Careful further nitration of (II) with nitric acid (*d* 1·5) in acetic acid at $< 60°$ afforded (probably) 2 : 7-*dinitro*-3 : 4-*di*-tert.-*butylacenaphthene* (V), which on oxidation gave the unexpected result of a 75% yield of the mononitro-anhydride (III). Analyses confirmed that no trace of a dinitronaphthalic anhydride was formed at any stage. This lends strong support to the view that the second substituted nitro-group enters the 7-position, although no such novel nitro-substitution has been recorded previously in the acenaphthene series. An alleged acenaphthene-7-sulphonic acid was described by Kalle and Co. (G.P. 248,994), who sulphonated acenaphthene with chlorosulphonic acid, and favoured this constitution because of its conversion by alkaline fusion into acenaphthylene. However, Dziewoński and Stolyhwo (*Ber.*, 1924, **57**, 1531) showed that oxidation of the sulphonic acid gave 2-sulphonaphthalene-1 : 8-dicarboxylic acid, thus indicating that the sulphonic group occupies the 1-position in the acenaphthene nucleus. Side-chain nitration is recorded in the naphthalene series; *e.g.*, Robinson and Turner (*J.*, 1932, 2015) prepared 4-methyl-1-nitromethylnaphthalene, which was oxidised to naphthalene-1 : 4-dicarboxylic acid.

The nitro-derivative (II) is reduced best by aqueous-alcoholic sodium hydrosulphite to yield 2-*amino*-3 : 4-*di*-tert.-*butylacenaphthene*, which is diazotisable with difficulty, in hydrochloric acid or nitrosylsulphuric acid, with much resin formation, but yields an *azo*-β-*naphthol* derivative.

Direct amination in the acenaphthene series does not appear to have been attempted. Under a variety of conditions, 1 mol. of acenaphthene reacted vigorously with 1·3 mols. of hydroxylamine hydrochloride and 2·2 mols. of aluminium chloride, but only a trace of amine was formed, detected by formation of the azo-β-naphthol derivative; 3 : 4-di-*tert.*-butylacenaphthene gave no identifiable base. It was, however, confirmed that a similar amination of benzene or toluene gave 5 to 6% yields of aniline or mixed toluidines, respectively (cf. Graebe, *Ber.*, 1901, **34**, 1778).

2-*Bromo*-3 : 4-*di*-tert.-*butylacenaphthene* (VI) was readily prepared in 83% yield by brominating 3 : 4-di-*tert.*-butylacenaphthene in chloroform, but care was necessary in order to obtain a specimen free from a trace of product which gives a persistent intense blue fluorescence in alcohols or acetic acid. The bromo-compound (VI) was unaffected by heating with excess of aqueous ammonia (*d* 0·88) in a sealed tube at 150°, and the nuclear position of the bromine atom was confirmed by oxidation of (VI) with sodium dichromate in acetic acid to the colourless 3-*bromo*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* (VII), which gives the naphthafluorescein reaction but does not condense with 2-hydroxythionaphthen. The anhydride (VII) gave *imides* and condensed with *o*-phenylenediamine to form the bright canary-yellow 2′(or 5′)-*bromo*-9′-*keto*-3′ : 4′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 3)-ψ-*indole*. The anhydride (VII) could not be prepared directly from 4 : 5-di-*tert.*-butylnaphthalic anhydride, which was unchanged by

the action of bromine alone or in chloroform or nitrobenzene at various temperatures, by excess of bromine and a little acetic acid at 150° in a sealed tube for 4 hours, or by excess of bromine in 10% fuming sulphuric acid at 100—120°. Francesconi and Bargellini (*Gazzetta*, 1902, **32**, 73) brominated naphthalic anhydride in fuming sulphuric acid.

The nitro-compound (II) could not be brominated, but further bromination of 2-bromo-3 : 4-di-*tert.*-butylacenaphthene in chloroform or carbon disulphide gave the 2 : *x*-*dibromo*-derivative; oxidation caused some loss of bromine and much resin formation, but orientation of the second bromine atom was not established, as the oxidation product gave inconsistent analytical data.

Unlike the nitro-group, nuclear-substituted bromine does not have an inhibiting effect on acenaphthenequinone formation. Mild oxidation converts 3-bromoacenaphthene into 3-bromoacenaphthenequinone (cf. Graebe and Guinsbourg, *Annalen*, 1903, **327**, 85; Guha, *J.*, 1931, 583). Restricted oxidation of 2-bromo-3 : 4-di-*tert.*-butylacenaphthene with sodium dichromate and acetic acid, and repeated extraction of the anhydride (VII) from the product with boiling aqueous sodium carbonate, gave 16% of 2-*bromo*-3 : 4-*di*-tert.-*butylacenaphthene-quinone* (VIII), from which small amounts of (VII) are difficult to remove. The use of ammonium dichromate has no advantage over sodium dichromate in this reaction (Daschevskii and Karischin, *Org. Chem. Ind. U.S.S.R.*, 1936, **1**, 729, claim a yield of 71·1% of acenaphthenequinone from acenaphthene). When (VI) was oxidised for 40 minutes, mixed crystals of (VII) and (VIII) were obtained, a similar phenomenon occurring in the oxidation of 3 : 4-di-*tert.*-butylacenaphthene (*loc. cit.*); mixed crystals of acenaphthenequinone and naphthalic anhydride are recorded by Kiprianov and Dashevskii (*J. Appl. Chem. Russia*, 1934, **7**, 944), who state that prolonged alkali extraction is necessary to obtain the quinone reasonably pure. Condensation of the quinone (VIII) with 2-hydroxythionaphthen was best effected in a mixture of acetic and hydrochloric acid (8 : 1) rather than by the alcoholic-alkali method recorded in G.P. 205,377 (Basler Chem. Fabrik in Basel). The resulting scarlet 2′(or 5′)-*bromo*-3′ : 4′-*di*-tert.-*butyl*-1 : 7′-*thionaphthenacenaphthenylindigo* (IX) shows no improvement in dyeing properties compared with the unbrominated analogue, and dyes cotton pink from a difficulty-formed bluish-violet alkaline hydrosulphite vat. Similar thioindigoid vat *dyes* were prepared by condensing the quinone (VIII) with 5-ethoxy- and 5-chloro-3-methyl-2-hydroxythionaphthen, severally.

Experimental.

M. ps. are corrected. Micro-analyses were carried out by Dr. G. Weiler and Dr. F. B. Strauss, of Oxford.

2-*Nitro*-3 : 4-*di*-tert.-*butylacenaphthene* (II).—(*a*) Nitric acid (*d* 1·5; 2·3 g., 1·2 mols.) was added to 3 : 4-di-*tert.*-butylacenaphthene (8 g.; 1 mol.) in acetic acid (40 c.c.) at room temperature, and the mixture heated gradually during 10 minutes to 60°. On cooling, the *mononitro*-derivative separated; it crystallised from alcohols, acetic acid, or acetic anhydride, in yellow prismatic needles, m. p. 144° (7·8 g.; 83·3%) (Found: C, 77·1; H, 8·0; N, 4·6. $C_{20}H_{25}O_2N$ requires C, 77·2; H, 8·0; N, 4·5%). No isomeride was found in the mother-liquors. Potassium nitrate and sulphuric acid were unsatisfactory for nitration, there being much frothing and charring.

(*b*) Diacetylorthonitric acid (Pictet and Genequand, *Ber.*, 1902, **35**, 2526) (9·6 g.; 8·2 c.c., equivalent to 1·3 mols. of HNO_3) was added all at once to a stirred mixture of finely-powdered 3 : 4-di-*tert.*-butylacenaphthene (10·4 g.; 1 mol.) suspended in acetic anhydride (25 c.c.) at 0°; a clear solution was formed, from which yellow needles separated progressively (8·5 g.; 76·6%).

2 : (?)7-*Dinitro*-3 : 4-*di*-tert.-*butylacenaphthene* (V).—Nitric acid (d 1·5; 2·3 g., 1·1 mols.) in acetic acid (5 c.c.) was added during 5 minutes to a solution of 2-nitro-3 : 4-di-*tert.*-butylacenaphthene, m. p. 144° (10 g., 1 mol.), in acetic acid (40 c.c.) at 40°; after the mixture had been heated slowly to 60° and kept at this temperature for 15 minutes, and then cooled, the *dinitro*-compound separated; it crystallised from acetic acid in pale yellow needles, m. p. 198° (decomp.) (8 g.; 70·2%) (Found: C, 67·5; H, 6·9; N, 8·0. $C_{20}H_{24}O_4N_2$ requires C, 67·4; H, 6·7; N, 7·9%). To avoid resin formation, the reaction temperature must not exceed 60°. The dinitro-compound was unchanged on boiling with aqueous sodium carbonate or ammonia, or with dilute mineral acids, but became resinous with hot aqueous or alcoholic alkali hydroxides; it could not be converted into the mononitro-derivative (II).

2-*Amino*-3 : 4-*di*-tert.-*butylacenaphthene*.—The 2-nitro-compound (II) (7 g.) was refluxed with a solution of sodium hydrosulphite (20 g.) in water (80 c.c.) and alcohol (30 c.c.) for 3 hours. After removal of the alcohol, the *base* separated in pale yellow leaflets, which crystallised from aqueous alcohol containing a trace of hydrosulphite in almost colourless prisms, m. p. 153° (5·2 g.; 83·5%) (Found: C, 84·9; H, 9·6; N, 5·2. $C_{20}H_{27}N$ requires C, 85·4; H, 9·6; N, 5·0%), which become brown in air. With concentrated hydrochloric acid, the hydrochloride was obtained in colourless needles, m. p. 220°. The *acetyl* derivative crystallised from alcohol in colourless needles, m. p. 257—258° (Found: N, 4·2. $C_{22}H_{29}ON$ requires N, 4·3%). The *phthalanil* separated from acetic acid in colourless prisms, m. p. 292—293° (Found: C, 81·7; H, 7·2. $C_{28}H_{29}O_2N$ requires C, 81·75; H, 7·05%). The *azo-β-naphthol* derivative, obtained in only low yield, crystallised from aqueous acetic acid in minute, dark brown needles, m. p. 175° (Found: C, 81·8; H, 7·1; N, 6·0. $C_{30}H_{32}ON_2$ requires C, 82·6; H, 7·3; N, 6·4%), which dissolved in cold concentrated sulphuric acid with a bluish-green colour.

3-*Nitro*-4 : 5-*di*-tert.-*butylnaphthalic Anhydride* (III).—(*a*) Sodium dichromate (35 g.) was added

during 30 minutes to a solution of 2-nitro-3 : 4-di-*tert.*-butylacenaphthene (10 g.) in acetic acid (250 c.c.) at 110°, and the mixture refluxed for a further 3 hours. On addition of ice-water, an almost colourless precipitate separated; it was collected, washed with warm water, and crystallised from acetic acid; colourless prisms, m. p. 183° (8·7 g.; 76·3%) (Found: C, 67·6; H, 5·9; N, 3·9. $C_{20}H_{21}O_4N$ requires C, 67·6; H, 5·9; N, 3·9%). 3-*Nitro*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* is moderately soluble in boiling 15% aqueous sodium carbonate. On fusion with resorcinol and zinc chloride, and addition to dilute aqueous ammonia, the anhydride gives a pale yellow solution with a strong green fluorescence, owing to naphthafluorescein formation. (III) was recovered unchanged on heating with nitric acid (*d* 1·5) in absence or presence of 25% fuming sulphuric acid at 95—100° for 1 hour.

(*b*) Pure 2 : (?)7-dinitro-3 : 4-di-*tert.*-butylacenaphthene (10 g.) was oxidised with sodium dichromate (40 g.) in boiling acetic acid (400 c.c.) for 5 hours to give colourless prisms, m. p. and mixed m. p. with the product from (*a*), 183° (7·5 g.; 75%) (Found: N, 4·0%).

(*c*) Finely ground 4 : 5-di-*tert.*-butylnaphthalic anhydride (5 g.) was warmed to 50° with excess of nitric acid (*d* 1·5; 8 g.) and then kept at room temperature for 2 hours. After dilution, the solid was collected and crystallised from acetic acid; colourless needles, m. p. 183° (4·1 g.; 71·7%), identical with those obtained by methods (*a*) and (*b*).

Derivatives of 3-*Nitro*-4 : 5-*di*-tert.-*butylnaphthalic Anhydride*.—On being refluxed with excess of aqueous ammonia (*d* 0·88) and a little alcohol for 1 hour, the anhydride gave 3-*nitro*-4 : 5-*di*-tert.-*butylnaphthalimide*, which crystallised from acetic acid in colourless prisms, or from alcohol in colourless needles, m. p. 288—289° (Found: C, 67·7; H, 6·3; N, 7·7. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·2; N, 7·9%), also obtained from 4 : 5-di-*tert.*-butylnaphthalimide (cf. *J.*, 1942, 562) and excess of nitric acid (*d* 1·5) at 40° for 10 minutes. The corresponding N-*methylimide*, prepared by boiling the anhydride in methyl alcohol with excess of 33% aqueous methylamine for 1 hour, crystallised from acetic acid in colourless prisms, m. p. 260° (Found: C, 68·2; H, 6·4; N, 7·6. $C_{21}H_{24}O_4N_2$ requires C, 68·5; H, 6·5; N, 7·6%). The 2 : 4-*dinitrophenylhydrazide* crystallised from acetic acid in pale yellow needles, m. p. 308—309° (Found: C, 58·7; H, 4·7. $C_{26}H_{25}O_8N_5$ requires C, 58·3; H, 4·7%). The anhydride (1 mol.) and *o*-phenylenediamine (1·4 mols.), refluxed in acetic acid for 15 minutes, afforded 2′(or 5′)-*nitro*-9′-*keto*-3′ : 4′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 3)-*ψ*-*indole* (IV), which crystallised from acetic acid or alcohol in bright yellow needles, m. p. 266—267° (Found: C, 72·6; H, 6·0; N, 9·7. $C_{26}H_{25}O_2N_3$ requires C, 73·1; H, 5·85; N, 9·8%).

2-*Bromo*-3 : 4-*di*-tert.-*butylacenaphthene* (VI).—Bromine (7·7 g.; 1·2 mols.) in chloroform (20 c.c.) was added during 5 minutes to a stirred solution of 3 : 4-di-*tert.*-butylacenaphthene (10·6 g.) in chloroform (100 c.c.) at room temperature. Hydrogen bromide was evolved, and after 1 hour the mixture was refluxed for 10 minutes; most of the chloroform was then removed, but care must be taken to add alcohol before all the chloroform is distilled, otherwise a trace of yellowish-green colouring matter with a very strong blue fluorescence in organic solvents, is formed, which is extremely difficult to remove on subsequent crystallisation. When pure, the *monobromo*-compound separated from alcohol in colourless prismatic needles, m. p. 137—138° (11·4 g.; 83·2%) (Found: C, 70·0; H, 7·5; Br, 22·6. $C_{20}H_{25}Br$ requires C, 69·6; H, 7·2; Br, 23·2%), which show no fluorescence in alcohols or acetic acid. A little soluble resin was also formed, but no isomeride was isolable. The bromo-derivative was unchanged on boiling with alcoholic picric acid, or on boiling with excess of aqueous ammonia (*d* 0·88) in a sealed tube at 150° for 4 hours. A resin only was obtained on attempted preparation from 2-amino-3 : 4-di-*tert.*-butylacenaphthene by the diazo-reaction, or on attempted nitration under various conditions.

2 : x-*Dibromo*-3 : 4-*di*-tert.-*butylacenaphthene*.—Bromine (2·8 g.; 1·2 mols.) in chloroform (15 c.c.) was added to a well-stirred solution of 2-bromo-3 : 4-di-*tert.*-butylacenaphthene, m. p. 137—138° (5 g., 1 mol.), in chloroform (60 c.c.) during 20 minutes. The mixture was stirred at room temperature for a further hour and then refluxed for 20 minutes, and most of the chloroform was removed; addition of alcohol precipitated a yellow resinous mass which solidified when kept at 0° for 12 hours. No fluorescence was noticed in alcohol (cf. the monobromo-derivative). Dissolution of the product in *tert.*-butyl alcohol at 50°, followed by careful dilution with water and standing for 48 hours gave cream needles, m. p. 110—120°, which crystallised from aqueous acetic acid in colourless prisms, m. p. 126°, of the *dibromo*-compound (3·6 g.; 58·5%) (Found: C, 56·6; H, 5·7; Br, 37·8. $C_{20}H_{24}Br_2$ requires C, 56·6; H, 5·7; Br, 37·7%). No higher brominated derivative could be isolated by treating 3 : 4-di-*tert.*-butylacenaphthene or its monobromo- or dibromo-derivative with excess of bromine in chloroform or carbon disulphide, the sole products formed being the above dibromo-compound and an intractable tar. Oxidation of the dibromo-compound with sodium dichromate and acetic acid under various conditions gave a resin and a low yield of alkali-soluble product which crystallised from aqueous acetic acid in pale yellow needles, m. p. varying between 155° and 175° (Found in these different specimens: Br, 21·5, 24·3, 27·5%).

2-*Bromo*-3 : 4-*di*-tert.-*butylacenaphthenequinone* (VIII) *and* 3-*Bromo*-4 : 5-*di*-tert.-*butylnaphthalic Anhydride* (VII).—(*a*) 2-Bromo-3 : 4-di-*tert.*-butylacenaphthene (10 g.) was refluxed with sodium dichromate (40 g.) in acetic acid (200 c.c.). After 40 minutes, addition to water gave a solid (10 g.) which was extracted twice with boiling 15% aqueous sodium carbonate and crystallised five times from aqueous acetic acid to give pale yellow prismatic needles (4 g.), m. p. 152—153° (Found: C, 63·6; H, 5·8; Br, 21·2. $C_{20}H_{21}O_2Br$,$C_{20}H_{21}O_3Br$ requires C, 63·0; H, 5·5; Br, 21·0%), which were probably mixed crystals of (VII) and (VIII), as condensation with 2-hydroxythionaphthen gave a red thioindigoid dye.

(*b*) When the reaction, as in (*a*), was extended by refluxing for 6 hours, and the resulting resinous solid extracted twelve successive times with boiling 15% aqueous sodium carbonate (1 l.), the combined extracts on acidification gave 3-*bromo*-4 : 5-*di*-tert.-*butylnaphthalic anhydride* (VII), which crystallised from aqueous acetic acid and then alcohol in colourless glistening leaflets, m. p. 184—185° (5·7 g.; 50·5%) (Found: C, 62·3; H, 5·5; Br, 20·6. $C_{20}H_{21}O_3Br$ requires C, 61·7; H, 5·4; Br, 20·6%). This colourless anhydride does not react with 2-hydroxythionaphthen, but gives the naphthafluorescein reaction on fusion with resorcinol and zinc chloride.

(*c*) Sodium dichromate (45 g.) was added all at once to 2-bromo-3 : 4-di-*tert.*-butylacenaphthene (15 g.) in acetic acid (200 c.c.) at 110°, and the reaction allowed to proceed without external heat for 10

minutes. Ice–water was added and the precipitate (15·5 g.) was extracted seven times with boiling 15% aqueous sodium carbonate; acidification gave the above anhydride (VII) (6·5 g.; 38·6%). The insoluble residue (*A*) was chromatographed, using alumina and benzene, with no further apparent separation except for the removal of a little resin, and finally it was crystallised from aqueous acetic acid in pale yellow needles, m. p. 162—163°, mainly of the quinone (VIII) (2·6 g.; 16%) (Found: C, 63·6; H, 5·6; Br, 21·2. $C_{20}H_{21}O_3Br$ requires C, 64·3; H, 5·6; Br, 21·45%), but still containing a little of the anhydride (VII).

Derivatives of 3-*Bromo*-4 : 5-di-*tert.*-*butylnaphthalic Anhydride*.—The *naphthalimide* crystallised from aqueous acetic acid in colourless, glistening needles, m. p. 314—315° (Found: N, 3·7; Br, 20·3. $C_{20}H_{22}O_3NBr$ requires N, 3·6; Br, 20·6%). The N-*methylimide* separated from aqueous alcohol in colourless, asbestos-like needles, m. p. 218—220° (Found: N, 3·3; Br, 20·0. $C_{21}H_{24}O_3NBr$ requires N, 3·5; Br, 19·9%). 2′(or 5′)-*Bromo*-9′-*keto*-3′ : 4′-*di*-tert.-*butyl*-8′-*azaphenalino*(7′ : 8′ : 2 : 3)-ψ-*indole* crystallised from much acetic acid in canary-yellow needles, m. p. 280—283° (Found: N, 5·7; Br, 17·7. $C_{26}H_{28}ON_2Br$ requires N, 6·1; Br, 17·35%).

Derivatives of 2-*Bromo*-3 : 4-*di*-tert.-*butylacenaphthenequinone*.—Condensation of the above oxidation product (*A*) with freshly prepared colourless 2-hydroxythionaphthen in a mixture of acetic and hydrochloric acid (8 : 1), after boiling for 5 minutes, gave 2′(or 5′)-*bromo*-3′ : 4′-*di*-tert.-*butyl*-1 : 7′-*thionaphthenacenaphthenylindigo* (IX), which was purified by boiling with alcohol and crystallisation of the insoluble residue from acetic acid; scarlet prisms, m. p. 274—275° (Found: C, 65·7; H, 4·9; S, 6·2. $C_{28}H_{25}O_2BrS$ requires C, 66·5; H, 4·95; S, 6·3%), which dissolve in cold concentrated sulphuric acid with a bluish-green colour and form a bluish-violet vat with aqueous-alcoholic sodium hydrosulphite. 2′(or 5′)-*Bromo*-5-*ethoxy*-3′ : 4′-*di*-tert.-*butyl*-1 : 7′-*thionaphthenacenaphthenylindigo* crystallised from acetic acid in red prisms, m. p. 236—238° (Found: Br, 14·5; S, 6·2. $C_{30}H_{29}O_3BrS$ requires Br, 14·6; S, 5·8%), which dissolve in concentrated sulphuric acid with a greenish-brown colour and form a brownish-violet vat with hydrosulphite. The 5-*chloro*-3-*methyl* analogue of (IX) crystallised from acetic acid in orange-red prisms, m. p. 340—343° (Found: S, 6·1; 5·037 mg. gave 3·07 mg. of AgCl + AgBr, $C_{29}H_{26}O_3ClBrS$ requires S, 5·8; AgCl + AgBr, 3·02 mg.), soluble in concentrated sulphuric acid with a brown colour and forming a brownish-violet hydrosulphite vat.

The author thanks Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

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[*Received, September 12th*, 1946.]

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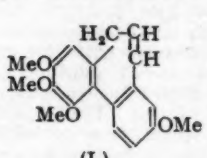
141. *Colchicine and Related Compounds. Part VI.* 3 : 4 : 5 : 6-*Dibenzcyclohepta*-1 : 3 : 5-*triene*.

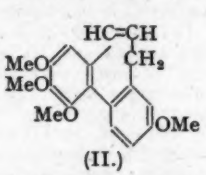
By J. W. COOK, G. T. DICKSON, and J. D. LOUDON.

3 : 4 : 5 : 6-Dibenz*cyclo*hepta-1 : 3 : 5-triene (IX) has been prepared, characterised and compared with deaminocolchinol methyl ether (I) which, in conformity with the structural relationship, it closely resembles in chemical properties. Evidence of the ease with which compounds of this type yield derivatives of phenanthrene on oxidation has been supplemented by isomerisation of (IX) to 9-methylphenanthrene.

SIMULTANEOUSLY with attempts to synthesise deaminocolchinol methyl ether, the present work was undertaken in order to ascertain whether certain properties of the compound, which led to its formulation as 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene (I), are in fact reproduced by the unsubstituted hydrocarbon of this structure. More particularly experimental evidence was required to decide whether, as was suggested in Part V (*J.*, 1945, 176), isomerisation of a dibenz*cyclo*heptatriene accounts for the isolation by Windaus of 9-methylphenanthrene from deaminocolchinol methyl ether following demethylation and distillation with zinc (*Annalen*, 1924, **439**, 59).



(I.)



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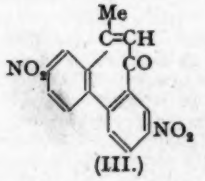

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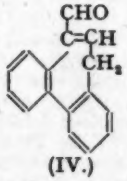
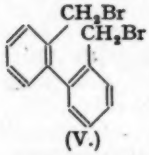


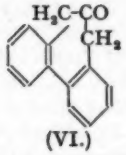
(IV.)

Comparatively little is known of the chemistry of 3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene and its derivatives. Kenner, who prepared from ωω′-dibromo-*oo*′-ditolyl a number of compounds containing this arrangement of carbon atoms (*J.*, 1913, **103**, 613; cf. Kenner and Turner, *J.*, 1911, **99**, 2101), pointed out that the ease of forming the seven-membered ring from this particular starting material was comparable with that found in the production of indane derivatives from xylylene dibromide and on steric grounds suggested analogy between the dibenz*cyclo*heptatriene and indene series. Similarly facile ring closure is implicit in the direct

formation of (III) by heating 2-bromo-5-nitroacetophenone with copper (Borsche and Herbet, *Annalen*, 1941, **546**, 293) and in the preparation of (IV), from the bisacetal of diphenyl-*oo'*-diacetaldehyde, described by Weitzenböck (*Monatsh.*, 1913, **34**, 199) who also showed that (IV) yields phenanthraquinone when oxidised in acetic acid with sodium dichromate. In all these cases a symmetrically substituted diphenyl is the actual or probable precursor of the dibenz*cyclo*heptatriene derivative in which, accordingly, a corresponding symmetry is retained. On the other hand deaminocolchinol methyl ether is not symmetrically substituted in the lateral rings and is accompanied by the isomeric compound (II) in at least two of the methods used for its preparation. Although at present no particular significance can be attached to the simultaneous formation of these two isomerides, since the structures of the compounds from which they were derived are incompletely known, yet it may be pointed out that the isomerides themselves contain a triad system and in their individual stability resemble the reluctant prototropy of $\alpha\gamma$-diarylpropenes (Ingold and Piggott, *J.*, 1922, **121**, 2381; Ingold and Shoppee, *J.*, 1929, 447) rather than the mobility of the triad system of indene.



(V.)



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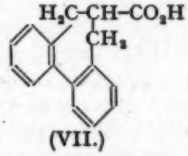
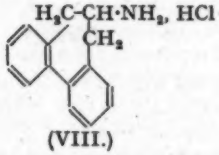
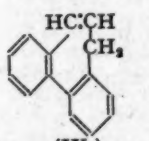


(VII.)

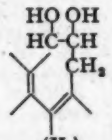


(VIII.)

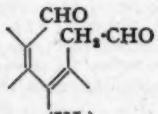
From the crude oil obtained by thermal decomposition of the amine hydrochloride (VIII), Kenner prepared a picrate of m. p. 137° which, on the basis of its analysis, he concluded was the picrate of dibenz*cyclo*heptatriene (IX). In view of the failure, recorded in Part V, to prepare a picrate from deaminocolchinol methyl ether, this result invited further inquiry. Kenner prepared (VIII) by two methods. In the first, the dibromide (V) was converted into the corresponding dinitrile which was cyclised by means of Thorpe's reaction followed by hydrolysis to the ketone (VI) and reduction of the ketoxime with sodium and alcohol. In the second, the dibromide was condensed with malonic ester, followed by hydrolysis and removal of carbon dioxide to form the acid (VII) which was then converted *via* the hydrazide, azide, and urethane into the required amine. Repetition of each of these methods, with an improved preparation of the dibromide and employing pressure-hydrogenation with Raney nickel as catalyst for reducing the ketoxime, gave in our hands consistent results which, however, differed slightly from Kenner's in respect of the m. ps. found for the amine hydrochloride and the corresponding acetylated base. Thermal decomposition of our hydrochloride gave an oil which was separated by distillation into a solid and a liquid fraction. The solid was identified as 9-methylphenanthrene by direct comparison and by formation of the picrate. The liquid was shown to contain dibenz*cyclo*heptatriene (IX) (cf. Experimental), but this compound was much more satisfactorily prepared by heating the acetylated base with phosphorus pentoxide in xylene following the procedure discovered by Cook and Graham (Part III; *J.*, 1944, 322) for deaminating *N*-acetylcolchinol methyl ether. The purified triene yielded a crystalline *dibromide* and absorbed approximately the correct amount of hydrogen for one double bond when hydrogenated in presence of palladium. We have not, however, been able to obtain from it a picrate, and this negative result is in accord with our experience with deaminocolchinol methyl ether. On the other hand it is by no means certain that Kenner's picrate (m. p. 137°) is to be explained by the presnce of 9-methylphenanthrene in the crude decomposition products of (VIII). Indeed, the m. p. of 9-methylphenanthrene picrate (152—153°) is in better agreement with that of a second picrate (m. p. 147—149°)—which depresses the m. p. of the first and was prepared by Kenner from the oily residue formed when the barium salt of (VII) was heated under diminished pressure. Repetition of this last experiment by us gave in fact some 9-methylphenanthrene.



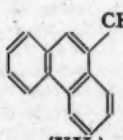
(IX.)



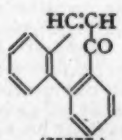
(X.)



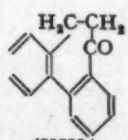
(XI.)



(XII.)



(XIII.)



(XIV.)

Oxidation of dibenz*cyclo*heptatriene (IX) reproduced in all essential respects the behaviour of deaminocolchinol methyl ether with corresponding oxidising agents (Part V). With osmium

tetroxide in ether the triene formed the *diol* (X) which by fission with lead tetra-acetate in benzene gave a gum, converted into 9-phenanthraldehyde (XII) on warming with a trace of sodium carbonate in ethanol. The presumed intermediate, namely the dialdehyde (XI), was not isolated. Oxidation of the triene with sodium dichromate in acetic acid gave phenanthrene-9-carboxylic acid and phenanthraquinone—products which may well represent successive stages of an oxidation course proceeding through the above diol and phenanthraldehyde. In addition a ketonic *by-product*, $C_{15}H_{10}O$, was also obtained, corresponding with a similar by-product, $C_{15}H_6O(OMe)_4$, isolated from deaminocolchinol methyl ether and regarded in Part V as an αβ-unsaturated ketone. In the present instance the structure (XIII) for this by-product was confirmed by its preparation from (IX) through the action of selenium dioxide and also by its quantitative hydrogenation with palladium as catalyst to the *ketone* (XIV). Oxidation of (XIV) and of its isomer (VI) afforded further examples of the ease with which the central seven-membered ring in this series of compounds undergoes oxidative degradation to a six-membered ring: in each case with sodium dichromate in acetic acid phenanthraquinone and some diphenic acid were produced.

The simultaneous production of the triene (IX) and 9-methylphenanthrene from (VIII) as described above, is not proof that the former product can be converted into the latter. Apart from some resinification the triene was unaffected by direct heating or by distillation from sodium ethoxide, while distillation under reduced pressure from anhydrous zinc chloride yielded only high-boiling products, presumably polymerides. On the other hand, when subjected to the treatment used by Windaus to remove the methoxyl groups from deaminocolchinol methyl ether—namely, heating with hydriodic acid and subsequent distillation from zinc dust—the triene first gave an iodinated product which at the second stage, or by distillation from sodium ethoxide, yielded 9-methylphenanthrene. Accordingly, dibenz*cyclo*heptatriene (IX) in the method of its preparation from the *N*-acetylated base, in its behaviour towards oxidation and reduction, in non-formation of a picrate and in its conversion into 9-methylphenanthrene, closely reflects the behaviour of deaminocolchinol methyl ether, which was formulated in Part V as the tetramethoxy-derivative.

Other synthetic approaches to dibenz*cyclo*heptatriene derivatives are under investigation in these laboratories. One route, on which some exploratory experiments had been carried out, was abandoned following the publication of a paper by Drake and Sweeney (*J. Org. Chem.*, 1946, **11**, 67) who showed that the acid, which we had also obtained, formed by hydrolysis of the product of the action of ethyl diazoacetate on phenanthrene, is not a dibenz*cyclo*heptatriene-carboxylic acid, but the alkali-stable dibenznorcaradienecarboxylic acid.

Experimental.

ωω'-Dibromo-oo'-ditolyl.—A gently boiling solution of *oo'*-ditolyl (46 g.) in carbon tetrachloride (400 c.c.), containing a small crystal of iodine and covered by a layer of water (100 c.c.), was exposed to the light of three 40-watt bulbs while a solution of bromine (84·5 g.) in carbon tetrachloride (150 c.c.) was slowly added (2 hours). After further heating (½ hour) the cooled solution was washed with dilute sodium hydroxide, dried, and concentrated. The product, which solidified on rubbing with ligroin, formed small colourless rhombs, m. p. 89—90°, yield 54% (Kenner *loc. cit.*, gives m. p. 87·5°).

1-*Amino*-3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-3 : 5-*diene Hydrochloride* (VIII).—(*a*) The corresponding urethane (Kenner, *loc. cit.*) was heated with concentrated hydrochloric acid in a sealed tube at 150° for 6 hours.

(*b*) The corresponding 1-ketoxime (0·82 g.; Kenner, *loc. cit.*) in ethanol (100 c.c.) was hydrogenated in presence of Raney nickel at 85°/64 atm. The base, precipitated as the picrate from an ether solution of the filtered concentrates, was recovered in ether and, after removal of the solvent, was treated with concentrated hydrochloric acid. In each case the hydrochloride was obtained as needles, m. p. 256—258°, from dilute hydrochloric acid (Kenner gives m. p. 287°) (Found: C, 73·4; H, 6·7. Calc. for $C_{15}H_{16}NCl$: C, 73·3; H, 6·5%). By shaking with dilute sodium hydroxide and acetic anhydride it yielded the *N*-acetyl derivative, colourless needles, m. p. 157—158° from aqueous ethanol (Kenner gives m. p. 147°) (Found: C, 81·1; H, 6·7. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·8%).

3 : 4 : 5 : 6-*Dibenz*cyclo*hepta*-1 : 3 : 5-*triene* (IX).—(*a*) The aforesaid *N*-acetyl compound (3·1 g.) in pure xylene (75 c.c.) was heated under reflux (½ hour) with phosphorus pentoxide (10 g.). Fractional distillation of the filtered solution gave the *triene* (68% yield) as a colourless mobile oil, b. p. 100—110° (air bath)/10 mm. (Found: C, 93·6; H, 6·4. $C_{15}H_{12}$ requires C, 93·8; H, 6·3%. Microhydrogenation with palladium black gave 0·85 double bond). The triene displayed no evidence of picrate formation when treated with picric acid in ethanol, but with bromine in acetic acid, followed by dilution and extraction with ether, it gave a *dibromide*, m. p. 90—91° from methanol (Found: C, 51·1; H, 3·5. $C_{15}H_{12}Br_2$ requires C, 51·2; H, 3·4%).

(*b*) In a similar experiment using the urethane in place of the *N*-acetyl compound, some unchanged urethane was recovered as the solid produced when the xylene concentrates were rubbed with ligroin. Evaporation of the ligroin solution gave a semi-solid which was washed with ethanol, giving an unidentified material, needles m. p. 322—325° (with sublimation) from 2-ethoxyethanol (Found: C,

83·2; H, 6·2; N, 5·8%). The concentrated ethanol washings from this material gave on distillation a small quantity of the triene, identified as the above dibromide, m. p. and mixed m. p. 89—90°.

(*c*) The hydrochloride (VIII; 0·35 g.) was heated in a sublimation tube at 320° (bath temp.; at 300° the compound slowly sublimes unchanged). The sublimate, dissolved in ether, was washed with dilute hydrochloric acid (which removes some unchanged hydrochloride) and recovered from the solvent. It distilled mainly between 80° and 115° (air bath)/0·1 mm., the later portion solidifying and giving 9-methylphenanthrene, m. p. and mixed m. p. 91°; picrate, m. p. and mixed m. p. 152—153°. The earlier oily fraction contained the triene as was shown by formation of the dibromide, m. p. and mixed m. p. 87—90°. A third small fraction, b. p. 175—185°/0·2 mm., was not investigated further beyond noting that it did not yield a picrate in ethanol.

Thermal decomposition of the barium salt of (VII). The barium salt, containing some un-neutralised barium hydroxide, was heated under reduced pressure. A yellow viscous oil slowly distilled [170—200° (bath temp.)/10 mm.] and solidified in the receiver. After purification by chromatography this furnished colourless needles, m. p. and mixed m. p. with 9-methylphenanthrene, 90—91°; the picrate had m. p. and mixed m. p. 153—154°.

Oxidation of the Triene (IX).—(a) *With sodium dichromate.* The triene (0·3 g.) in acetic acid (1·6 c.c.) was treated with sodium dichromate (0·98 g.) in acetic acid (2·3 c.c.), and the solution was heated for 1½ hours at 100°. After dilution, a chloroform extract of the mixture was washed with dilute sodium carbonate, dried, and concentrated. The residue, dissolved in benzene–ligroin (1 : 1), was separated on a column of alumina into a feebly adsorbed pale-pink band and a more strongly adsorbed orange band. The eluate of the former gave, on evaporation, a gum which solidified when rubbed with ligroin, yielding 3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-1 : 3 : 5-*trien*-7-*one* (XIII), m. p. 83—84° from benzene–ligroin (Found: C, 87·4; H, 4·9. $C_{15}H_{10}O$ requires C, 87·4; H, 4·9%. Microhydrogenation with palladium black gave 0·98 double bond). The compound gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 231—232° (Found: C, 65·3; H, 3·6. $C_{21}H_{14}O_4N_4$ requires C, 65·3; H, 3·6%), and dissolved in strong sulphuric acid to a bright yellow solution.

The orange band was eluted with benzene–ethanol from which was recovered phenanthraquinone, m. p. and mixed m. p. 200—202° from benzene (diazine, from *o*-phenylenediamine, m. p. and mixed m. p. 218°). The carbonate washings of the chloroform solution gave, on acidification, phenanthrene-9-carboxylic acid, m. p. and mixed m. p. 249—251° after purification.

(b) *With selenium dioxide.* A solution of the triene (0·19 g.) in xylene (1 c.c.) was heated under reflux with selenium dioxide (0·125 g.) for 6 hours. The gum obtained from the filtered and concentrated solution was dissolved in ether, washed with dilute sodium hydroxide, then with water, dried, recovered, and distilled. Dibenz*cyclo*heptatrien-7-one was obtained as a yellow oil, b. p. 115° (bath-temp.)/0·2 mm., which solidified in the receiver, m. p. and mixed m. p. with the above sample 83—84°.

(c) *With osmium tetroxide.* A solution of the triene (0·5 g.) in dry ether (25 c.c.) was treated with osmium tetroxide (0·75 g.) in dry ether (25 c.c.). After 3 days, the residue obtained by removing the solvent was heated under reflux with a solution of hydrated sodium sulphite (8 g.) in water (75 c.c.) and methanol (100 c.c.) for 3 hours. Undissolved solid was collected and well washed with methanol, filtrate and washings being combined and concentrated. The concentrates were diluted with water and extracted with ether from which, after further washings with water and drying, the product was recovered. cis-1 : 2-*Dihydroxy*-3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-3 : 5-*diene* (X) formed colourless prisms, m. p. 121° from methanol (Found: C, 79·8; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·7; H, 6·2%).

Scission with lead tetra-acetate. Lead tetra-acetate (120 mg.) was added, portionwise and with shaking, to a solution of the above diol (60 mg.) in pure dry benzene (18 c.c.) maintained at 40°. The mixture was heated to boiling and then left at room temperature for 1 hour. After filtration the benzene solution was washed with water, dried, and evaporated. The resulting gum, which did not crystallise from ethanol, slowly deposited pale yellow needles of 9-phenanthraldehyde after being warmed with a little sodium carbonate in ethanol. The aldehyde had micro-m. p. 99—100° (positive test with 2 : 4-dinitrophenylhydrazine), and was oxidised by dropwise addition of 6% potassium permanganate (0·3 c.c.) to its solution (11 mg.) in pure acetone (1 c.c.). After clarification with sulphurous acid, the solution was extracted with chloroform from which phenanthrene-9-carboxylic acid, m. p. and mixed m. p. 245—248°, was recovered by means of aqueous sodium carbonate and was purified by vacuum sublimation. The chloroform residues contained some unchanged aldehyde.

3 : 4 : 5 : 6-*Dibenz*cyclo*hepta*-3 : 5-*dien*-2-*one* (XIV.)—The unsaturated ketone (XIII; 170 mg.), hydrogenated in acetic acid (7 c.c.) with palladium black as catalyst (50 mg.), absorbed the calculated quantity of hydrogen in 45 minutes at room temperature. After removal of the solvent from the filtered solution, the product was obtained as pale yellow hexagonal prisms, m. p. 85—86° from benzene–ligroin (m. p. depressed to 55—75° by admixture with starting material) (Found: C, 86·5; H, 5·7. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%); the 2 : 4-*dinitrophenylhydrazone* had m. p. 240° (decomp.) (Found: C, 65·1; H, 4·1. $C_{21}H_{16}O_4N_4$ requires C, 65·0; H, 4·1%). The ketone was oxidised by adding a solution of sodium dichromate (0·5 g.) in acetic acid (1·5 c.c.) to its solution (115 mg.) in acetic acid (1 c.c.) and subsequent heating under reflux for 1 hour. After dilution with water, extraction with chloroform, and washing the extract with aqueous sodium carbonate, the recovered neutral fraction was identified as phenanthraquinone, m. p. and mixed m. p. 204—205° from benzene (diazine, m. p. and mixed m. p. 218—219°). Acidification of the carbonate washings gave diphenic acid, m. p. and mixed m. p. 220—223° from ethanol.

The same products were obtained from similar oxidation of 3 : 4 : 5 : 6-dibenz*cyclo*hepta-3 : 5-dien-1-one (VI).

Conversion of the Triene (IX) *into* 9-*Methylphenanthrene.*—A solution of the triene (0·16 g.) in acetic acid (4·2 c.c.) and hydriodic acid (1·5 c.c.; *d* 1·7) was heated under reflux for 4 hours. The oil obtained by evaporation was saturated towards bromine and contained (non-ionic) iodine. Since attempted purification by distillation in a vacuum caused liberation of iodine, the crude material was used in two portions: (*a*) Chromatography gave no evidence of the presence of 9-methylphenanthrene at this stage, but, when the eluted and recovered material was distilled from sodium ethoxide, the distillate consisted

of almost pure 9-methylphenanthrene, m. p. and mixed m. p. 90—92°. (*b*) When the oil was mixed with zinc dust and distilled at atmospheric pressure, much charring ensued; the distillate, which contained only a little solid, was again mixed with zinc dust, heated at 260° for several hours, and re-distilled. The product was a pale yellow oil, b. p. 90—100° (air bath)/10 mm., of which the later portion solidified and was separately crystallised from methanol giving 9-methylphenanthrene, m. p. and mixed m. p. 89—90° (picrate, m. p. and mixed m. p. 153—154°). The earlier oily portion of the distillate was saturated towards bromine and was analysed after renewed distillation in which only the first runnings were taken (Found: C, 92·9; H, 6·8. Calc. for $C_{13}H_{14}$: C, 92·8; H, 7·2%). It was possibly dibenz*cyclo*heptadiene.

Action of Ethyl Diazoacetate on Phenanthrene.—This was carried out by a procedure based on that use by Buchner and Schottenhammer (*Ber.*, 1920, **53**, 868) for a similar reaction with mesitylene. The higher-boiling fractions, after reaction, were hydrolysed with alcoholic potash and gave an acid which, after vacuum sublimation and then crystallisation from ethanol, formed colourless needles, m. p. 259° (Found: C, 81·1; H, 5·15. Calc. for $C_{16}H_{12}O_2$: C, 81·3; H, 5·1%). This was obviously the acid, m. p. 257·4—258°, obtained in better yield by Drake and Sweeney (*loc. cit.*) and shown by them to be dibenznorcaradienecarboxylic acid. In agreement with these authors, we found the acid to be moderately resistant to oxidation by alkaline permanganate and by chromic acid in acetic acid. The *methyl* ester, obtained with ethereal diazomethane, formed colourless elongated plates, m. p. 144—145° (from methanol) (Found: C, 81·3; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

We thank the Carnegie Trust for the Universities of Scotland for a Scholarship which has enabled one of us (G. T. D.) to take part in this investigation. The microanalyses were by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, September 13th*, 1946.]

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142. *Reactions of Carbinols in the Presence of Alkali. Part I. The Reduction of Ketones by Primary Alcohols.*

By G. H. HARGREAVES and L. N. OWEN.

The reduction is described of several aliphatic ketones to the corresponding secondary alcohols by the action of simple aliphatic primary alcohols in the presence of concentrated aqueous alkali at 240°. The mechanism of the reaction is discussed.

THE literature contains several references to the reduction of ketones by primary alcohols in the presence of alkali. Zagoumenny (*Annalen*, 1877, **184**, 174) obtained benzhydrol by heating benzophenone with alcoholic potassium hydroxide, and Montagne (*Rec. Trav. chim.*, 1908, **27**, 327; 1912, **31**, 298; 1916, **35**, 258; 1920, **39**, 339; 1922, **41**, 703; *Ber.*, 1916, **49**, 2243) showed that the ease of reduction of many substituted benzophenones depended upon the nature of the substituents. Palfray and Sabetay (*Compt. rend.*, 1932, **194**, 79; 1934, **198**, 1513; 1936, **203**, 1523) and Mastagli (*ibid.*, 1937, **204**, 1656; **205**, 802; *Ann. Chim.*, 1938, **10**, 281) reduced aromatic ketones, and a number of aromatic and higher aliphatic aldehydes, to the corresponding secondary and primary alcohols by boiling with potassium benzyloxide in benzyl alcohol, a process evidently analogous to that under discussion. Rubin (*J. Amer. Chem. Soc.*, 1944, **66**, 2075) has reported the reduction of 3-anisylhexan-4-one to the carbinol by alcoholic potassium hydroxide. The method has also been applied in the porphyrin field (Fischer and Zeile, *Annalen*, 1929, **468**, 98) and for the reduction of alicyclic bridged-ring ketones (Allen, Jones, and VanAllan, *J. Org. Chem.*, 1946, **11**, 268).

Few examples are known, however, of the reduction of aliphatic ketones by this method. The classical instance of the reduction of methylheptenone to methylheptenol was recorded by Tiemann (*Ber.*, 1898, **31**, 2991) and confirmed by Doeuvre (*Bull. Soc. chim.* 1929, **45**, 351), and Schicht (G.P. 327,510) described a process whereby the higher aliphatic ketones, such as behenone, were reduced by the action of primary alcohols in the presence of aqueous alkali. No systematic study appears to have been made of the reduction of simple aliphatic ketones under such conditions, and for reasons concerned with the subject matter of Parts II and III (following papers) it was necessary to establish the generality of the reaction.

For this purpose, di*iso*propyl ketone was treated with equimolecular quantities of methyl, ethyl, and *n*-propyl alcohols in the presence of a concentrated aqueous solution of either sodium or potassium hydroxide at 240° in a rocking autoclave. Hydrogen was liberated and, with one exception (methanol with potassium hydroxide), reduction to di*iso*propylcarbinol occurred in all experiments, better results being obtained throughout by the use of sodium hydroxide. Formic acid could not be isolated from the experiments in which methanol was used, but acetic and propionic acids were obtained when ethyl and *n*-propyl alcohol, respectively, were the reducing agents, the yield of carbinol then being *ca.* 55%. In connection with the scission

experiments to be described in Part III, the reduction of methyl *n*-butyl ketone by ethanol and potassium hydroxide was proved to give methyl-*n*-butylcarbinol and acetic acid, whilst *n*-propyl *n*-butyl ketone and *n*-butanol gave *n*-propyl-*n*-butylcarbinol and *n*-butyric acid. It was also shown that methyl *n*-hexyl ketone was reduced to the carbinol by butanol and aqueous sodium hydroxide. In all these experiments, considerable amounts of high-boiling materials, probably unsaturated ethers, were obtained; clearly, the yield of carbinol is likely to be adversely affected by the necessity of carrying out the reductions in a closed system, with consequent facilitation of secondary reactions.

Two experiments were also performed with acetophenone, which was reduced by methanol and by *n*-amyl alcohol, in the presence of aqueous sodium hydroxide, to give a small yield of phenylmethylcarbinol, accompanied by much resin, probably a styrene polymer.

Since the boiling points of the aliphatic ketones were not widely different from those of the corresponding carbinols, the quantitative separation of the ketone–carbinol mixtures was impracticable, and their ketone content was estimated by precipitation of the 2 : 4-dinitrophenylhydrazone, which was purified by chromatographic adsorption on alumina. Control experiments, on artificial ketone–carbinol mixtures, showed the yield of purified derivative to be at least 90%.

Although it has long been known (Dumas and Stas, *Annalen*, 1840, **35**, 129; Hell, *ibid.*, 1884, **223**, 269; Nef, *ibid.*, 1904, **335**, 302; Carroll, *J. Physical Chem.*, 1918, **22**, 128; Weizmann and Garrard, *J.*, 1920, **117**, 324; Fry *et al.*, *J. Amer. Chem. Soc.*, 1924, **46**, 2268; 1926, **48**, 958; 1928, **50**, 1122, 1130; Reid, Worthington, and Larcher, *ibid.*, 1939, **61**, 99) that primary alcohols, when heated alone with aqueous alkali, undergo dehydrogenation to give the corresponding acid, with liberation of two mols. of hydrogen: $R{\cdot}CH_2{\cdot}OH \longrightarrow R{\cdot}CO_2H + 2H_2$, it is unlikely that this reaction is directly concerned in the reduction of ketones, since di*iso*propyl ketone was not reduced when heated with hydrogen and aqueous sodium hydroxide under the appropriate conditions. It may, of course, be postulated that the reduction occurs by " nascent " hydrogen, but a more likely explanation would appear to be that the reaction is of the Meerwein–Ponndorf–Verley type (cf. Rubin, *loc. cit.*; Wilds, " Organic Reactions," 1944, **2**, 178) and may be represented as $R{\cdot}CH_2{\cdot}OH + R'{\cdot}CO{\cdot}R'' \rightleftharpoons R{\cdot}CHO + R'{\cdot}CH(OH){\cdot}R''$. Under the strongly alkaline conditions, however, the equilibrium represented by the above equation will not be maintained, owing to a further reaction undergone by the aldehyde, *viz.*, conversion into the corresponding acid, with evolution of one mol. of hydrogen. Although it might appear that, in the case of a simple aliphatic aldehyde, condensation to an aldol or resin would supervene, it has been established by Fry and Schulze (*J. Amer. Chem. Soc.*, 1926, **48**, 958) that the introduction of acetaldehyde vapour into a mixture of sodium and potassium hydroxides at 250° results in a 90% yield of acetic acid, with the liberation of hydrogen; furthermore, the conversion of sebacic semialdehyde into sebacic acid with concentrated aqueous alkali has now been observed (Part II, following paper). In the reductions by benzyl alcohol, recorded by Palfray and Sabetay (*loc. cit.*) and by Mastagli (*loc. cit.*), the formation of benzoic acid from the intermediate benzaldehyde could clearly occur through a Cannizzaro reaction.

The overall reaction is, therefore, $R{\cdot}CH_2{\cdot}OH + R'{\cdot}CO{\cdot}R'' \longrightarrow R{\cdot}CO_2H + R'{\cdot}CH(OH){\cdot}R'' + H_2$, but it is evident that the direct dehydrogenation of the primary alcohol may occur simultaneously; this would be reflected in a yield of hydrogen greater than that of carbinol, and also, unless an excess of primary alcohol is used, in the presence of unchanged ketone in the reaction products. Both of these features were observed in the majority of the present experiments, and the formation of the high-boiling by-products indicates also that further secondary reactions occur under the vigorous conditions employed (cf. Guerbet, *Compt. rend.*, 1901, **133**, 1220; 1902, **134**, 467; 1908, **146**, 298, 1405).

Experimental.

(Light petroleum refers to the fraction of b. p. 40—60°.)

Methyl-n-butylcarbinol.—This was prepared in 60% yield by the method of Grignard and Fluchaire (*Ann. Chim.*, 1928, **9**, 15); b. p. 139—140°, $n_D^{19°}$ 1·4147.

Methyl n-Butyl Ketone.—Oxidation of the carbinol (20 g.) with the calculated amount of chromic acid (cf. *idem*, *ibid.*) gave a 50% yield of ketone, b. p. 128—130°, $n_D^{16°}$ 1·4041. For larger-scale work (100-g. batch) it was preferable to prepare the ketone directly by condensation of acetic anhydride and -butylmagnesium bromide at − 70°, according to the method of Newman and Booth (*J. Amer. Chem. Soc.*, 1945, **67**, 154).

n-*Propyl-n-butylcarbinol.*—This was obtained in 65% yield by the method of Bouveault and Locquin (*Bull. Soc. chim.*, 1906, **35**, 644); b. p. 77—78°/15 mm., $n_D^{17°}$ 1·4257. The *α-naphthylurethane* crystallised

from light petroleum in fluffy needles, m. p. 61—62° (Found: N, 4·85. $C_{19}H_{31}O_2N$ requires N, 4·7%).

n-*Propyl* n-*Butyl Ketone*.—Oxidation of the carbinol in acetone solution with chromic acid gave the ketone (80%), b. p. 167—169°, $n_D^{14°}$ 1·4173 (cf. Bouvealt and Locquin, *loc. cit.*). The 2 : 4-*dinitrophenylhydrazone* crystallised from light petroleum in orange needles, m. p. 41° (Found: N, 18·4. $C_{14}H_{20}O_4N_4$ requires N, 18·2%).

Estimation of Ketones in Ketone–Carbinol Mixtures.—A portion of the mixture (*ca.* 1 g., accurately weighed) in ethanol (5 c.c.) was shaken for 2 minutes with an excess of aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate, the solution diluted with water (100 c.c.), allowed to stand for ½ hour, and then extracted five times with 50-c.c. portions of benzene (light petroleum can be used if the derivative is sufficiently soluble in it). The combined extracts were chromatographed on a column of alumina (60 × 2·5 cm.), and the main band cut out as soon as it had separated. The derivative was recovered by elution with ether, the solvent removed, and the residue dried and weighed; the m. p. was usually only a few degrees below that of a recrystallised sample.

Reduction of Aliphatic Ketones.—The ketone (0·5 mol.), primary alcohol (0·5 mol.), alkali hydroxide (220 g.), water (150 c.c.), and an emulsifier (0·3 g. of palmitic acid) were shaken in an autoclave for 3 hours at 240°. After cooling, the gas was released and measured, and the contents of the autoclave were then diluted with water and extracted with ether to obtain the neutral products, which were fractionated. The main fraction, consisting of the ketone–carbinol mixture, was analysed for ketone content by the method described above; di*iso*propylcarbinol was identified as the phenylurethane, m. p. 96—99°; methyl-*n*-butyl-, *n*-propyl-*n*-butyl-, and methyl-*n*-hexyl-carbinols as the α-naphthylurethanes, m. ps. 61°, 61°, and 57—58°, respectively, not depressed on admixture with the authentic derivatives. High-boiling products were encountered in all experiments; *e.g.*, from the reduction of methyl *n*-hexyl ketone by butanol there was obtained a fraction (15 g.), b. p. 225—235°/20 mm., $n_D^{22°}$ 1·4772, which was unsaturated, but showed no ketonic or alcoholic properties. Acid products were isolated from the aqueous portion by acidification with sulphuric acid and ether extraction, acetic, propionic, and *n*-butyric acids being identified, after distillation, as the *p*-bromophenacyl esters, m. ps. 85°, 61°, and 63° respectively. The results are summarised in the table.

					Ketone–carbinol mixture.					
Ketone.	Alcohol.	Alkali.	H_2 (l.).	Acid (g.).	G.	B.p.	$n_D^{18°}$.	Ketone (g.).	Carbinol (g.).	Yield of carbinol (%).
$COPr^{\beta}_2$	MeOH	NaOH	9	—	28	125—136°	1·4105	18	10	17
,,	,,	KOH	11	—	32	124—128	1·4034	32	0	0
,,	EtOH	NaOH	9	5	40	127—140	1·4178	10	30	52
,,	,,	KOH	10	3	34	127—137	1·4118	14	20	34
,,	*n*-PrOH	NaOH	5	9	40	122—140	1·4178	8	32	55
,,	,,	KOH	2·5	2	34	120—137	1·4094	27	7	12
$COMeBu^{\alpha}$	EtOH	KOH	3	1	11·5	134—145	1·4141	0·5	11	22
$COPr^{\alpha}Bu^{\alpha}$	*n*-BuOH	KOH	1·5	4	30	70—83 *	1·4223	10	20	31
$COMe{\cdot}C_6H_{13}(n)$	*n*-BuOH	NaOH	2	5	13	171—184	1·4243	1 †	12	19

* At 18 mm.

† The 2 : 4-*dinitrophenylhydrazone*, a yellow microcrystalline powder, m. p. 78—79°, from aqueous ethanol, was not that of the expected methyl *n*-hexyl ketone, but appeared to be derived from a carbonyl compound $C_7H_{14}O$ (Found: C, 52·15; H, 6·0; N, 19·0. $C_{13}H_{18}O_4N_4$ requires C, 53·0; H, 6·15; N, 19·0%). The absorption spectrum in alcohol, kindly determined by Dr. E. A. Braude, showed $\lambda_{max.}$ 2250, 2560, and 3580 A. (log ε: 4·23, 4·02, and 4·36 respectively) consistent with its formulation as a derivative of an aldehyde $C_6H_{13}{\cdot}CHO$ (cf. Braude and Jones, *J.*, 1945, 498). This is unlikely to be *n*-heptaldehyde (2 : 4-dinitrophenylhydrazone, m.p. 107°) and its identity is obscure.

Reduction of Acetophenone.—Acetophenone (60 g., 0·5 mol.), primary alcohol (0·5 mol.), sodium hydroxide (220 g.), water (150 c.c.), and palmitic acid (0·3 g.) were shaken in an autoclave at 240°, and the products isolated in the usual way. With methanol, heating being maintained for 5 hours, the hydrogen amounted to 12 l. The neutral products gave a main fraction (13 g.), b. p. 101—109°/18 mm., $n_D^{18°}$ 1·5233, from which was obtained the phenylurethane, m. p. 92—93°, of phenylmethylcarbinol. Much high-boiling material was present. The acid products contained benzoic acid, m. p. 122° (presumably a decomposition product), and a trace of formic acid, separated as the lead salt.

Reduction with *n*-amyl alcohol for 3 hours gave hydrogen (2 l.), *n*-valeric acid (5 g.), identified as the *p*-bromophenacyl ester, m. p. 63°, and a neutral fraction (4 g.), b. p. 104—109°/19 mm., $n_D^{17°}$ 1·5109, which gave the phenylurethane of phenylmethylcarbinol, m. p. 92—93°. A large amount of high-boiling material (45 g., b. p. 135—220°/1 mm.) was also formed.

The authors wish to express their thanks to Monsanto Chemicals Ltd. (Ruabon) for a grant to one of them (G. H. H.) during the course of the work described in this and the two following papers.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, September 17th*, 1946.]

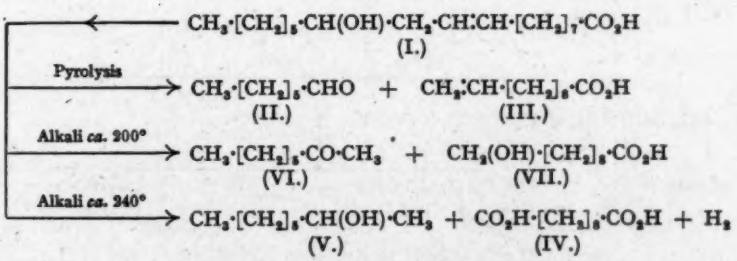
143. *Reactions of Carbinols in the Presence of Alkali. Part II. The Scission of Ricinoleic Acid.*

By G. H. Hargreaves and L. N. Owen.

It has been confirmed that the alkaline scission of ricinoleic acid does not occur below 180°. The initial products are probably methyl *n*-hexyl ketone and 10-hydroxydecanoic acid; at higher temperatures (*ca.* 240°) these interact to give methyl-*n*-hexylcarbinol, sebacic acid, and hydrogen (cf. Part I), only one mechanism thus being necessary to explain both the "ketone-producing" and the "carbinol-producing" scissions. Sebacic semialdehyde has been obtained in pure crystalline form; it undergoes dehydrogenation to sebacic acid on treatment with alkali at 240°.

The scission of ricinoleic acid (I) on heating was apparently first observed in 1827 by Bussy and Lecanu (*Compt. rend.*, **21**, 84; *J. Pharm. Chim.*, **1845**, **8**, 321); by pyrolysis of ricinoleates they obtained "oenanthol," subsequently identified as *n*-heptaldehyde (II) (cf. Bouis, *Ann. Chim. Phys.*, **1855**, **44**, 77). It was shown by Krafft (*Ber.*, 1877, **10**, 2034; 1878, **11**, 2018) that undec-10-enoic acid (III) was also formed in this reaction. Bouis (*Compt. rend.*, 1851, **33**, 143; 1859, **41**, 603) had also investigated the pyrolysis of castor-oil, which is mainly glyceryl triricinoleate, in the presence of excess alkali, and by vigorous heating had obtained sebacic acid (IV) and a volatile "capryl" alcohol, which was eventually shown to be methyl-*n*-hexylcarbinol (V). The scission was extensively investigated during the next few years (cf. Neison, *J.*, 1874, **27**, 507, 837) and although the results obtained, owing to insufficient attention to experimental conditions, were somewhat conflicting, it was shown that the alkaline scission gave methyl *n*-hexyl ketone (VI) in addition to the carbinol, though the yield of ketone diminished with increase of reaction temperature; this last observation, as will be seen subsequently, is of considerable importance. Much later, Lee (*Chem. Abstr.*, 1917, **11**, 3027) reported the evolution of hydrogen during the production of carbinol, and it was only in 1941 that Houpt (U.S.P. 2,217,515) showed that the ketone is accompanied by 10-hydroxydecanoic acid (VII). Attention has also been paid in recent years to the determination of the optimum conditions for the production of either ketone or carbinol (B.PP. 534,321, 534,322; U.S.PP. 2,182,056, 2,217,516, 2,318,762; Houpt, *loc. cit.*; Adams and Marvel, *Org. Synth.*, Coll. Vol. I, 2nd ed., p. 366) and it is clear that ricinoleic acid in the presence of alkali undergoes scission to ketone and hydroxy-acid at *ca.* 200°, whilst the carbinol and sebacic acid are the main products at temperatures above 240°.

Three types of scission are therefore known, which may be summarised according to the scheme below:

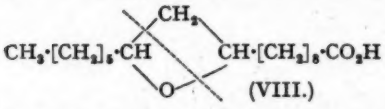


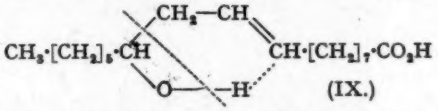
Other products, which have occasionally been reported, result from secondary reactions; octene, for example, is derived by dehydration of the carbinol.

The outstanding exception to the above conclusions is to be found in a claim by Svetlov and Vulfson (*J. Appl. Chem. Russia*, **1936**, **9**, **1613**) for the preparation of methyl-*n*-hexylcarbinol in 90% yield by the alkaline scission of castor-oil at a reaction temperature of only 112—117°. We have been unable to repeat these results, and have shown that no appreciable reaction occurs below 180°; there would appear to be little doubt that the reaction observed by the Russian workers occurred at the surface of the gas-heated copper vessel, the temperature of which would be considerably higher than the main bulk of the semi-solid reaction mixture.

Little has hitherto been known of the mechanisms by which ricinoleic acid undergoes the above types of fission. Barbot (*Bull. Soc. chim.*, **1935**, **2**, 895, 1438; *Ann. Chim.*, **1939**, **11**, 519; cf. Isikawa *et al.*, *Chem. Abstr.*, 1940, **34**, 3240) postulated the intermediate formation of an

oxide (VIII) or a hydrogen-bonded structure (IX), followed by scission, in the direction shown, to give *n*-heptaldehyde and undec-10-enoic acid. These suppositions, however, in reality offer


(VIII.)


(IX.)

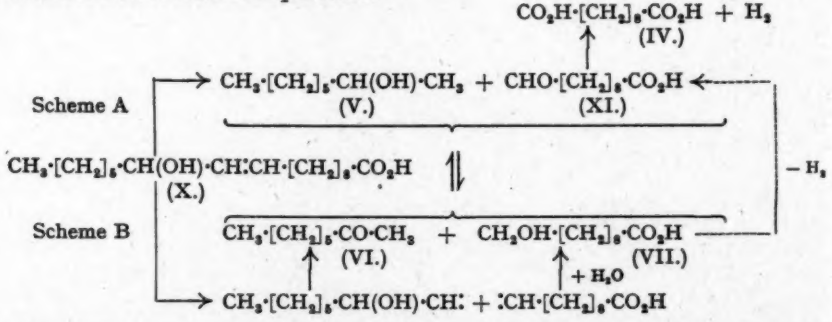
little explanation of this neutral pyrolytic scission, and, furthermore, shed no light on the more difficult problem of the scission under alkaline conditions.

It has been recognised for some time that the ethylenic linkage in ricinoleic acid is capable of migration towards the hydroxyl group; barium ricinoleate, for instance, on being heated is transformed into barium 12-ketostearate, a change which involves a double migration of the ethylenic linkage:

$$\cdot CH(OH)\cdot CH_2\cdot CH{:}CH\cdot \longrightarrow \cdot CH(OH)\cdot CH{:}CH\cdot CH_2\cdot \longrightarrow \cdot C(OH){:}CH\cdot [CH_2]_2\cdot \longrightarrow \cdot CO\cdot [CH_2]_3\cdot$$

This isomerisation may also be brought about by heating esters of ricinoleic acid with metal catalysts (Belopolski and Maximov, *Chem. Zentr.*, 1937, II, 1694; Hanford, Schreiber, and Gray, U.S.P. 2,340,745). Isomerisation to the intermediate acid (X), followed by scission at the ethylenic linkage, was considered probable by Noorduyn (*Chem. Zentr.*, 1920, I, 731) and by Verkade (*Rec. Trav. chim.*, 1927, **46**, 200) in order to explain the formation of the C_8 alcohol and ketone; Panjutin (*J. Russ. Phys. Chem. Soc.*, 1928, **60**, 1) unsuccessfully sought evidence for the presence of (X) by examination of the residues from partly pyrolysed ricinoleic esters.

If double-bond migration from the $\beta\gamma$- to the $\alpha\beta$-position is the first step in the alkaline scission, it would be anticipated that $\alpha\beta$-ethylenic carbinols in general would also undergo fission with alkali; this is indeed the case, for it has now been shown that such carbinols undergo both types of fission when heated with concentrated alkali to the appropriate temperature (see Part III, following paper). There is therefore little doubt that preliminary isomerisation occurs with ricinoleic acid, but it is still possible to envisage several routes for the succeeding reactions. In Scheme A, hydrolytic fission of the ethylenic linkage in the rearranged acid (X) to give the carbinol (V) and sebacic semialdehyde (XI), followed by conversion of the latter into sebacic acid (IV), explains the formation of the products obtained above 240°. Furthermore, since aldehydes can be reduced by aluminium alkoxides, a similar reaction may well occur in the presence of alkali-metal alkoxides, so that the primary products (V) and (XI) would be capable of transformation into the ketone (VI) and hydroxy-acid (VII), thus accounting also for the products obtained at the lower temperature.



An obvious difficulty about Scheme A is this fact that the ketone-producing scission occurs at a temperature appreciably lower than that required for the production of the carbinol, since it is possible, by careful control of the temperature, to obtain the ketone practically free from carbinol. This strongly suggests that the primary products are the ketone and hydroxy-acid, the formation of which may perhaps be visualised as though occurring by scission at the ethylenic linkage, followed by rearrangement of one fragment to give the ketone, and hydration of the other to give the hydroxy-acid, according to Scheme B. The production of the carbinol, sebacic acid, and hydrogen at the higher temperature can then be explained in a simple manner as a direct reduction of the ketone by the primary alcoholic group present in the acid; the generality of this type of reaction for aliphatic ketones and primary alcohols has already been demonstrated (Part I, preceding paper), and it has now been shown to apply to the case under discussion, since the treatment of a mixture of methyl *n*-hexyl ketone and 10-hydroxydecanoic acid with 60%

sodium hydroxide solution at 240° resulted in the formation of methyl-*n*-hexylcarbinol, sebacic acid, and hydrogen.

Sebacic semialdehyde, a postulated intermediate in both of the above schemes, has now been obtained in a pure crystalline form, m. p. 56—57° (cf. Braun and Keller, *Ber.*, 1933, **66**, 215), by ozonisation of undec-10-enoic acid. In agreement with the suggested mechanisms, it is converted into sebacic acid when heated with concentrated aqueous alkali at 240°.

A probable side reaction, represented by the broken line in the diagram, is the direct conversion of the hydroxy-acid into sebacic acid (cf. Part I). This would account for the observation that the carbinol is never obtained completely free from small amounts of ketone.

Account must still be taken, however, of an early observation, due to Marckwald and McKenzie (*Ber.*, 1901, **34**, 469), which we have confirmed, that the methyl-*n*-hexylcarbinol obtained by the alkaline fission of ricinoleic acid shows slight optical activity ($[\alpha]_D^{20°}$ — 0·1°). This may be due to a trace of impurity, since commercial ricinoleic acid was used in these experiments,* or it may indicate that, if the temperature is raised rapidly to 240°, scission can also occur to some extent according to the first mechanism, in which case the asymmetric character of the carbinol group would be maintained.

Experimental.

(Light petroleum refers to the fraction of b. p. 40—60°.)

Minimum Scission Temperature of Ricinoleic Acid.—Treatment of either ricinoleic acid (20 g.) or castor oil (20 g.) with 30% aqueous sodium hydroxide (18 c.c.) was carried out in a "Pyrex" flask under reflux, heated in an oil-bath maintained at 125—130° for 3 hours. The proportions of materials were those used by Svetlov and Vulfson (*loc. cit.*). Neither ketone nor carbinol could be detected in the reaction products, which yielded only unchanged ricinoleic acid. The addition of copper bronze to the reactants did not affect the result.

The experiments were then repeated, the condenser being arranged for distillation, and the contents of the flask vigorously stirred whilst the temperature of the oil-bath was gradually raised. Water was added to the reaction mixture at a rate equal to that at which it was lost by distillation. The minimum bath temperature at which scission occurred, as indicated by the appearance of methyl *n*-hexyl ketone in the distillate, was 180—200°, the corresponding internal temperature being 175—195°. The presence of a small quantity of copper bronze accelerated the scission, the effect probably being due to increased heat conductivity.

"Ketone-producing" Scission of Ricinoleic Acid.—Sodium hydroxide (500 g.) and water (200 c.c.) were heated in a 5-l. "Pyrex" flask immersed in an oil-bath maintained at 195—200°. The flask was fitted with a mercury-sealed stirrer, condenser, and receiver, so arranged that both liquid and gaseous products could be collected. Commercial ricinoleic acid (500 g.) was added during 3 hours, accompanied by water to replace that lost by distillation, vigorous stirring being maintained throughout. Heating, stirring, and addition of water were continued for a further 4 hours. The distillate contained an upper layer of methyl *n*-hexyl ketone (115 c.c.) containing traces of carbinol; the small amount of hydrogen evolved (2·5 l.) indicated the formation of only 7% of carbinol. The residue in the flask, after cooling, was dissolved in water (4 l.) and acidified with sulphuric acid. The oil was collected, and after standing for several days had partly solidified; the solid was obtained by filtration (36 hours at 15 mm.) and then freed from most of the remaining oil by pressing on porous tile. Recrystallisation from ether–light petroleum gave needle-clusters of 10-hydroxydecanoic acid (67 g.), m. p. 73°.

Reduction of Methyl n-Hexyl Ketone by 10-Hydroxydecanoic Acid.—The ketone (40 g.), hydroxy-acid (60 g.), sodium hydroxide (220 g.), and water (150 c.c.) were shaken in an autoclave at 240° for 3 hours. After cooling, the gas (2·5 l.) was released and shown by analysis to contain 85% hydrogen, 10% nitrogen, 1% oxygen, and *ca.* 3% hydrocarbons. (Nitrogen and oxygen are clearly derived from the air space in the autoclave.) The neutral products, isolated by ether extraction, gave, in addition to much high-boiling material, a main fraction (8 g.), b. p. 175°, $n_D^{17°}$ 1·4253. This contained 7% of unchanged methyl *n*-hexyl ketone (estimated as the 2 : 4-dinitrophenylhydrazone, m. p. 58°; cf. Part I, p. 752), but was mainly methyl-*n*-hexylcarbinol (α-naphthylurethane, m. p. 57—58°), the yield of which was thus 7·5 g. (18%). Acidification of the aqueous residues with sulphuric acid precipitated sebacic acid (25 g., 40%), which crystallised from water in plates, m. p. 131°.

Sebacic Semialdehyde.—A solution of undec-10-enoic acid (22 g.) in methylene dichloride (150 c.c.) was treated with ozonised oxygen at room temperature until no further absorption took place. The solution was then gradually added, with vigorous stirring and cooling, to a suspension of zinc dust (15 g.) in 30% aqueous acetic acid (200 c.c.). When the reaction had subsided, the mixture was heated on the steam-bath for 1 hour (the remaining methylene dichloride being allowed to escape through an air condenser), and then cooled, acidified to Congo-red with hydrochloric acid, and extracted with chloroform. After removal of solvent, the residual semi-solid material was distilled under reduced pressure, and gave a main fraction (12·0 g.), b. p. 150°/0·1 mm., which crystallised in the receiver as a hard white mass, m. p. 56—57°, unchanged on recrystallisation from acetone–light petroleum, from which it separated in glistening white plates (Braun and Keller, *loc. cit.*, gave m. p. 40—60°) (Found: C, 64·25; H, 9·5. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·7%). The semicarbazone, recrystallised from ethanol, formed nodules, m. p. 170° (Braun and Keller, *loc. cit.*, gave m. p. 155°) (Found: N, 17·0. Calc. for $C_{11}H_{21}O_3N_3$: N,

* The purification of ricinoleic acid is very laborious, and it is doubtful whether it has ever been obtained entirely free from traces of other acids.

17·3%). The *oxime* crystallised from methanol in prisms, m. p. 111° (Found: N, 7·1. $C_{10}H_{19}O_3N$ requires N, 7·0%).

Dehydrogenation of Sebacic Semialdehyde by Alkali—The semialdehyde (3 g.) was finely powdered and added to a hot solution of sodium hydroxide (6 g.) in water (4 c.c.). The semi-solid mass of sodium salt was thoroughly broken up, and the mixture transferred to a small autoclave and kept at 250° for 3 hours. After cooling, the product was dissolved in water, filtered, and acidified with sulphuric acid, yielding a precipitate (2·4 g.) of crude sebacic acid, m. p. *ca.* 120°, which after purification by sublimation at 100°/0·0001 mm. gave the pure acid (1·6 g.), m. p. and mixed m. p. 131°.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, September 17th*, 1946.]

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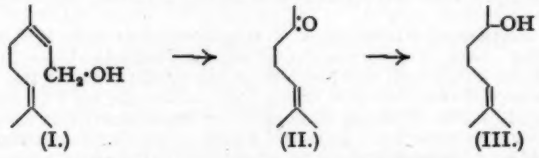
144. *Reactions of Carbinols in the Presence of Alkali. Part III. The Scission of αβ-Ethylenic Carbinols.*

By G. H. HARGREAVES and L. N. OWEN.

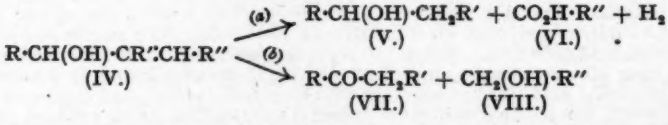
Oct-2-en-4-ol and 6-*ethyldec*-6-*en*-5-*ol* have been found to undergo both the "ketone-producing" and "carbinol-producing" types of fission, shown by ricinoleic acid, on treatment with alkali at 180—240° (cf. Part II).

THE mechanism for the alkaline scission of ricinoleic acid, discussed in Part II (preceding paper), involves a preliminary isomerisation of the ethylenic linkage from the βγ- to the αβ-position (with reference to the carbinol group). Since the carboxyl group in the acid does not take any essential part in the reaction, it would be anticipated that simple ethylenic carbinols would also undergo fission under similar conditions. The literature contains one well-known example of such a reaction, *viz.*, the treatment of geraniol (I) with concentrated alcoholic alkali at 150° to give methylheptenol (III) (Barbier, *Compt. rend.*, 1898, **126**, 1423; Tiemann, *Ber.*, 1898, **31**, 2991). According to Doeuvre (*Bull. Soc. chim.*, 1929, **45**, 351; cf. Tiemann, *loc. cit.*) the scission actually gives methylheptenone (II) as primary product, which is then reduced by the ethanol:



(I.) (II.) (III.)

This example, however, is not strictly comparable with ricinoleic acid, since geraniol contains a primary alcoholic group, and oct-2-en-4-ol (IV; R = *n*-Bu; R′ = H, R″ = Me) was therefore chosen for the investigation. This compound was unaffected by 60% potassium hydroxide solution at temperatures up to 175°, but treatment with the same reagent in a rocking autoclave at 240° resulted in the evolution of hydrogen (40%), and the formation of methyl-*n*-butylcarbinol (V; R = *n*-Bu, R′ = H) (38%) and acetic acid (VI; R″ = Me) (4%), the low recovery of acid being partly due to the difficulty of its isolation. The products of this reaction correspond precisely with those expected from a carbinol-producing scission (*a*), and the isolation of a small amount of methyl *n*-butyl ketone (VII; R = *n*-Bu, R′ = H) (4%) indicates the occurrence also of the ketone-producing scission (*b*), though it was impracticable to confirm the presence of the traces of ethanol (VIII; R″ = Me) which should also have been formed. The comparatively low yields of degradation products, which were accompanied by a considerable amount of



high-boiling material, are probably due in part to the necessity of carrying out the reaction on the ethylenic carbinol (b. p. 175°) in a closed system, with consequent facilitation of side reactions; with the non-volatile sodium ricinoleate, the neutral products can be removed by distillation during the course of the reaction. It was therefore of interest to use an ethylenic carbinol of higher boiling point, on which the scission could be investigated at atmospheric pressure. The choice of such a carbinol is restricted not only by availability but also by

consideration of the ease of separation of the possible degradation products, but a suitable substance was found in *6-ethyldec-6-en-5-ol* (IV; R = *n*-Bu, R′ = Et, R″ = *n*-Pr) which was synthesised by the condensation of 2-ethylhex-2-en-1-al with *n*-butylmagnesium bromide. The ketone-producing scission was brought about by treatment of this carbinol (b. p. 225°) with 60% aqueous potassium hydroxide at a bath temperature of 190—200°. Slow distillation occurred, but no gas was evolved, and the distillate yielded unchanged carbinol (25%), *n*-propyl *n*-butyl ketone (VII; R = *n*-Bu, R′ = Et) (22%), and *n*-butanol (VIII; R″ = *n*-Pr) (19%). The temperature at which this scission took place compared well with that required for the production of methyl *n*-hexyl ketone from ricinoleic acid (180—200°). No trace of products corresponding to the carbinol-producing scission (*a*) could be detected.

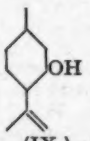
6-Ethyldec-6-en-5-ol was then shaken with 60% aqueous alkali in an autoclave at 240°. Scission (*a*) was shown to have occurred by the formation of hydrogen (45%) and the isolation from the reaction products of *n*-propyl-*n*-butylcarbinol (V; R = *n*-Bu, R′ = Et) (31%), identified as the α-naphthylurethane, and *n*-butyric acid (VI; R″ = *n*-Pr) (21%); small amounts of *n*-butanol (2%) and *n*-propyl *n*-butyl ketone (17%), which were also present, were evidently formed from scission (*b*).

An attempt was made to prepare an αβ-ethylenic carbinol from 2-ethylhex-2-en-1-al and *n*-octylmagnesium bromide, but dehydration occurred on distillation of the product, to give a 70% yield of a compound which was probably *di-(5-ethyltetradec-4-en-6-yl) ether*, $[n\text{-}C_8H_{17}\cdot CH(CEt{:}CH\cdot CH_2\cdot CH_2\cdot CH_3)]_2O$; it was unaffected by aqueous alkali at 250°. n-*Propyl*-n-*octylcarbinol*, which would have been one of the fission products from the expected ethylenic carbinol, was synthesised by the condensation of *n*-octylmagnesium bromide and *n*-butaldehyde.

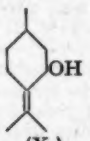
The mechanism of the alkaline scission of αβ-ethylenic carbinols is clearly similar to that of ricinoleic acid (Part II), and this has been confirmed by the reductions, described in Part I, of methyl *n*-butyl ketone with ethanol to give methyl-*n*-butylcarbinol, and of *n*-propyl *n*-butyl ketone with *n*-butanol to give *n*-propyl-*n*-butylcarbinol, the primary alcohols being simultaneously converted into acetic and *n*-butyric acids, respectively, and hydrogen being liberated. The ketone (VII) and primary alcohol (VIII) would thus appear to be the primary products, which at the higher temperature interact to give carbinol (V), acid (VI), and hydrogen, the overall mechanism corresponding to Scheme B (Part II, p. 754).

With regard to the scission of geraniol, to which reference was made above, since this is a primary alcohol and carries a substituent in the β-position, the " ketone-producing " scission would give acetaldehyde and methylheptenol (III) (corresponding to the ketone and primary alcohol, respectively, from the ethylenic carbinols previously considered) whereas from a " carbinol-producing " scission ethanol and methylheptenone (II) would be obtained. If, therefore, the scission of geraniol is comparable with that of the other ethylenic carbinols, methylheptenol may be a *primary* product of the scission, not derived by reduction of methylheptenone; the formation of the latter as a primary product would involve the mechanism of Scheme A rather than Scheme B.

Reference must also be made to the action of alkali on the βγ-ethylenic alcohol, *iso*pulegol (IX), which gives 3-methyl*cyclo*hexanol (XI) (*Ber. Schimmel*, 1913, October, p. 91). This evidently proceeds by initial isomerisation into pulegol (X); the formation of (XI) can then be



(IX.)



(X.)

(XI.)

explained either by a direct scission of Type A, or by a scission of Type B, in which case the primary products, 3-methyl*cyclo*hexanone and *iso*propyl alcohol, would interact to give 3-methyl*cyclo*hexanol and acetone.

The investigations described in the present paper are being extended to simple βγ-ethylenic carbinols.

Experimental.

Oct-2-en-4-ol.—To a stirred ethereal solution of butylmagnesium bromide (from 24 g. of magnesium), freshly distilled crotonaldehyde (70 g.), in ether, was added dropwise during 1 hour, with ice cooling. After being stirred for a further hour at 0°, the complex was decomposed by the addition of ammonium chloride (120 g.) and ice, and dilute sulphuric acid was added to break the emulsion. The ethereal layer

was removed, the aqueous portion was extracted with fresh ether, and the combined extracts were washed, dried, evaporated, and distilled to give oct-2-en-4-ol (85 g., 66%) as a mobile oil, b. p. 83°/20 mm., 175°/760 mm., $n_D^{15°}$ 1·4435 (Hurd, Greengard, and Pilgrim, *J. Org. Chem.*, 1937, **2**, 381, obtained a 55% yield; cf. also Karasev and Khabarova, *J. Gen. Chem. Russia*, 1940, **10**, 1641). No phenylurethane could be obtained from the carbinol, which appeared to dehydrate on standing with phenyl *iso*cyanate, but it gave a 3 : 5-*dinitrobenzoate*, which crystallised from aqueous alcohol in plates, m. p. 54° (Found : N, 8·25. $C_{15}H_{18}O_6N_2$ requires N, 8·7%).

Alkaline Degradation of Oct-2-en-4-ol.—(i) The alcohol was recovered almost quantitatively after refluxing, with vigorous stirring, with 40% sodium hydroxide or 60% potassium hydroxide for 3 hours. Scission therefore does not occur below 175°.

(ii) Oct-2-en-4-ol (50 g.), potassium hydroxide (220 g.), water (150 c.c.), and stearic acid (0·5 g., emulsifier) were heated in a rocking autoclave at 240° for 3 hours. After cooling, hydrogen (3·5 l.) was released, and the contents of the autoclave dissolved in water. The neutral products, isolated by ether extraction, gave a fraction (16·5 g.), b. p. 134—148°, $n_D^{18°}$ 1·4170, consisting mainly of methyl-*n*-butylcarbinol, identified as the α-naphthylurethane, m. p. and mixed m. p. 61°; it also contained 8% of methyl *n*-butyl ketone, estimated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 106° (for method of estimation, see Part I, p. 752). The yield of carbinol was thus 15 g.(38%), agreeing well with the 40% yield of hydrogen. A high-boiling fraction (10 g.), b. p. 150—220°/20 mm., was not further investigated. The aqueous residues, acidified with sulphuric acid, and extracted with ether, gave a fraction (1 g.), b. p. 100—120°, consisting largely of acetic acid, identified as the *p*-bromophenacyl ester, m. p. 85°.

6-*Ethyldec*-6-*en*-5-*ol.*—To a stirred ethereal solution of *n*-butylmagnesium bromide (from 24 g. of magnesium), cooled to 10°, was added freshly distilled 2-ethylhex-2-en-1-al (126 g.) in an equal volume of ether, during 1 hour. The mixture was stirred for a further hour and then refluxed for ½ hour, cooled to 0°, and the complex decomposed by the addition of ammonium nitrate (180 g.) and ice. After acidification with dilute sulphuric acid, ether extraction yielded 6-*ethyldec*-6-*en*-5-*ol* (122 g., 66%), b. p. 120—122°/10 mm., 225°/760 mm., $n_D^{16°}$ 1·4563 (Found : C, 78·1; H, 12·95. $C_{12}H_{24}O$ requires C, 78·2; H, 13·1%). No phenylurethane could be obtained, dehydration occurring on treatment with phenyl *iso*cyanate.

Alkaline Degradation of 6-*Ethyldec*-6-*en*-5-*ol.*—(i) The compound (20 g.), potassium hydroxide (24 g.), water (16 c.c.), and stearic acid (0·3 g.) were heated in a "Pyrex" flask immersed in an oil-bath maintained at 190—200°. The flask was fitted with a mercury-sealed stirrer, inlet tube, and condenser, receivers being arranged to collect both liquid and gaseous products. After 10 c.c. of water had distilled, water was allowed to enter the reaction flask at a rate equal to that at which it was collected. Heating was maintained for 4 hours, after which the distillate, consisting of water (60 c.c.) with an upper immiscible liquid (15 c.c.), was extracted with ether. The extracts were washed and dried, and, after careful evaporation of solvent, distillation yielded 3 main fractions : (*a*) 1·5 g., b. p. 100—130°, $n_D^{17°}$ 1·4035; (*b*) 3 g., b. p. 166—168°, $n_D^{17°}$ 1·4184; (*c*) 5 g., b. p. 113—121°/13 mm., $n_D^{19°}$ 1·4518. Fraction (*a*) consisted largely of *n*-butanol, identified as the α-naphthylurethane, m. p. and mixed m. p. 71°. Fraction (*b*) was *n*-propyl *n*-butyl ketone, and gave the 2 : 4-dinitrophenylhydrazone, m. p. 38°, not depressed on admixture with an authentic specimen, m. p. 41° (cf. Part I, p. 752). Fraction (*c*) was unchanged ethyldecenol. The yields of *n*-butanol and *n*-propyl *n*-butyl ketone were thus 19% and 22% respectively, uncorrected for recovered ethylenic carbinol. The residue in the reaction flask was acidified with dilute sulphuric acid and extracted with ether, which yielded a small quantity of unchanged ethyldecenol, but no trace of acid products; the complete absence of the "carbinol-producing" scission was also indicated by the observation that no hydrogen was evolved during the reaction.

(ii) 6-Ethyldec-6-en-5-ol (50 g.), potassium hydroxide (220 g.), water (150 c.c.), and stearic acid (0·5 g). were heated in a rocking autoclave for 3 hours at 240°. Hydrogen (2·75 l.) was then released from the cooled vessel, after which the neutral and acid products were isolated as previously described. The former, on distillation, gave (*a*) 0·5 g., b. p. 100—140°, containing *n*-butanol, identified as the α-naphthylurethane, m. p. 71°; (*b*) 17 g., b. p. 168—178°, $n_D^{18°}$ 1·4250, a mixture of *n*-propyl-*n*-butylcarbinol (α-naphthylurethane, m. p. 61—62°) with 35% of *n*-propyl *n*-butyl ketone, estimated as the 2 : 4-dinitrophenylhydrazone, m. p. 41°; (*c*) 20 g. of high-boiling residue, b. p. > 200°, which was not further investigated. The acid products on distillation gave *n*-butyric acid (5 g.), b. p. 71—78°/16 mm., identified as the *p*-bromophenacyl ester, m. p. and mixed m. p. 62°. The yields of *n*-propyl-*n*-butylcarbinol, *n*-butyric acid, and hydrogen were thus 31%, 21%, and 45% respectively.

Attempted Preparation of 5-*Ethyltetradec*-4-*en*-6-*ol.*—*n*-Octylmagnesium bromide was prepared from *n*-octyl bromide (97 g.) and magnesium (12 g.) in ether, the reaction being completed by refluxing for ½ hour. 2-Ethylhex-2-en-4-al (63 g.) was added to the cooled solution, and the product isolated by the procedure already described. On distillation it yielded a liquid (79 g., 68%), b. p. 166°/23 mm., $n_D^{18°}$ 1·4682, which showed unsaturation towards bromine water and neutral permanganate, and was recovered unchanged after treatment at 250° with concentrated sodium or potassium hydroxide solution. It was probably *di*-(5-*ethyltetradec*-4-*en*-6-*yl*) *ether* (Found : C, 83·45; H, 13·5. $C_{16}H_{32}O$ requires C, 79·9; H, 13·4; $C_{32}H_{62}O$ requires C, 83·05; H, 13·5%).

n-*Propyl*-n-*octylcarbinol.*—To a stirred ethereal solution of *n*-octylmagnesium bromide (from 2·3 g. magnesium) was added *n*-butaldehyde (7 g.) in ether, during 10 minutes. After being stirred for 2 hours, the mixture was refluxed for ½ hour, cooled to 0°, and decomposed with ice and ammonium chloride (15 g.). Isolation with ether gave n-*propyl*-n-*octylcarbinol* (6 g., 35%), b. p. 130—132°/19 mm., $n_D^{18°}$ 1·4365 (Found : C, 77·2; H, 13·8. $C_{12}H_{26}O$ requires C, 77·35; H, 14·05%).

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[*Received, September 17th*, 1946.]

145. *A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part I. The Monofluoro-5-aminoacridines.*

By J. H. Wilkinson and I. L. Finar.

The four isomeric monofluoro-derivatives of 5-aminoacridine have been prepared. Owing to the comparative inaccessibility of *o*-fluoroaniline an alternative route to the 1-fluoro-derivative *via o*-bromofluorobenzene has been investigated. As anticipated, the new derivatives possessed properties closely resembling those of the chlorine analogues, though the 1-fluoro-compound exhibited a number of anomalies.

The study of fluorine-substituted chemotherapeutic agents seems to have been somewhat neglected, only a comparatively small number having been described. The antibacterial properties of a series of aromatic acids have been investigated by Hager and Starkey (*J. Amer. Pharm. Assoc.*, 1942, **32**, 44), who have shown that fluorine substitution generally produced a slight increase in activity with but little effect on the toxicity. Magidson and Trawin (*J. Gen. Chem. Russia*, 1941, **11**, 243) have reported that 2-fluoro-5-(4-diethylamino-1-methylbutyl)-amino-7-methoxyacridine (the fluorine analogue of mepacrine) was inactive against Plasmodia, but no details of the antibacterial activity are given. The Russian workers do, however, state that it was highly toxic because of hydrolysis. In view of the comparative paucity of information concerning this aspect of the organic chemistry of fluorine, we considered it of interest to prepare a number of fluorine-substituted 5-aminoacridines since the parent compound has powerful antiseptic properties (Rubbo, Albert, and Maxwell, *Brit. J. Exp. Path.*, 1942, **23**, 69).

The monofluoro-compounds described in this paper were prepared by ring closure of the corresponding fluorodiphenylamine-2-carboxylic acids followed by conversion of the resulting 5-chloroacridines into aminoacridines by the method of Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5).

Preparation of Fluorodiphenylamine-2-carboxylic Acids.—(a) via *Fluoroanilines.* Thermal decomposition of the corresponding nitrobenzenediazonium borofluorides prepared by the method of Balz and Schiemann (*Ber.*, 1927, **60**, 1186) gave yields of 55% and 40% respectively of the *m*- and *p*-fluoronitrobenzenes which were reduced catalytically to the fluoroanilines in *ca.* 90% yield. These underwent the Ullmann condensation with *o*-iodobenzoic acid to give 3′- and 4′-*fluorodiphenylamine-2-carboxylic acids* in 64% and 81% yields respectively.

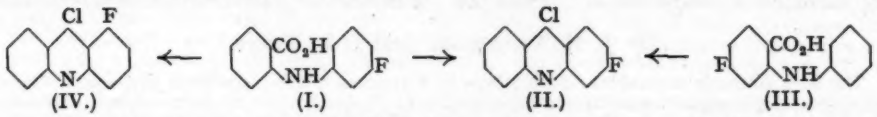
o-Nitrobenzenediazonium borofluoride, however, decomposed vigorously giving a large quantity of a black porous substance from which only about 4% of the required *o*-fluoronitrobenzene could be isolated (cf. Bennett, Brooks, and Glasstone, *J.*, 1935, 1821). Owing to the hazardous nature of this decomposition, no further investigation of the reaction was undertaken. The method of Swarts (*Bull. Acad. roy. Belg.*, 1914, 178) whereby a 6% yield of the ortho-isomer was obtained on nitration of fluorobenzene, was rejected owing to the laborious nature of the separation involved. The alternative route to *o*-fluoroaniline *via* a modified Hofmann degradation of *o*-fluorobenzamide (Rinkes, *Chem. Weekblad*, 1919, **16**, 212; Schiemann and Baumgarten, *Ber.*, 1937, **70**, 1416) was not pursued, as we found it possible to prepare 2′-*fluorodiphenylamine-2-carboxylic acid* in satisfactory yield by method (b).

(b) via o-*Bromofluorobenzene.* *o*-Bromofluorobenzene, prepared from *o*-bromoaniline *via* the diazonium borofluoride, condensed with anthranilic acid in the presence of cuprous chloride according to the method of Goldberg (G.P. 173,523) to give 2′-fluorodiphenylamine-2-carboxylic acid. When this condensation was performed in amyl alcohol a yield of 38% was obtained, but replacement of this reaction medium by *cyclo*hexanol resulted in an increase to 52%.

Preparation of 5-Chlorofluoroacridines.—These compounds were prepared by ring closure of the fluorodiphenylamine-2-carboxylic acids by means of phosphoryl chloride. Whereas the 2′- and 4′-substituted acids gave 5-*chloro*-1- and -3-*fluoroacridines* respectively in practically quantitative yields, the 3′-fluoro-acid (I) gave a mixture of the 2- and 4-substituted 5-chloroacridines since both ortho- and para-closure (Goldberg and Kelly, *J.*, 1946, 102) occur simultaneously. Lehmstedt and Schrader (*Ber.*, 1937, **70**, 838) have reported that negative substituents (*e.g.*, NO_2, Cl) in the 3′-position gave a ratio of ortho- to para-closure of 75 : 25, whereas a positive substituent (*e.g.*, methyl) gave about 20 : 80. Subsequently, however, Gleu and Nitzsche (*J. pr. Chem.*, 1939, **153**, 200) pointed out an error in the orientation of the methylacridones obtained by these workers, the true ratio in the case of the methyl substituted compounds being 80 : 20. Our experience with fluorine in the 3′-position differs from these results since the ratio of ortho- to para-closure was about 40 : 60.

5-*Chloro*-2-*fluoroacridine* (II) was separated from its isomer (IV) by fractional crystallisation

from alcohol. It proved to be identical with the product obtained by ring closure of *5-fluorodiphenylamine-2-carboxylic acid* (III) (see Experimental).



Owing to its very high solubility in practically all organic solvents, 5-chloro-4-fluoroacridine (IV) could not be obtained in a pure state. As it proved possible, however, to separate the 2- and 4-fluoro-5-aminoacridine hydrochlorides by virtue of their differing solubilities in water, we did not pursue the problem of separating the chlorofluoroacridines.

Properties of the Fluoro-5-aminoacridines.—These bases closely resembled 5-aminoacridine and the corresponding chloro-derivatives in physical properties, although *1-fluoro-5-aminoacridine* exhibited a number of anomalies. The accompanying table summarises the properties in which it differs from its isomers and from the chloro- and methyl analogues.

Physical Properties of Substituted 5-Aminoacridines.

Position of Substituent.	M. p. Substituent.			pK_a value. Substituent.			Solubility in alcohol (g. per 100 c.c.) (20°). Substituent.
	F.	Cl.[1]	Me.	F.	Cl.[4]	Me.[4]	F.
1	307°	235°	197° [2]	8·5	8·3	10·2	0·3
2	276	277	230—231 [3]	9·3	9·0	10·2	2·8
3	280	288—289	252 [1]	9·3	8·8	10·0	3·5
4	266	270	248—249 [1]	9·2	8·4	10·0	3·0

[1] Wilkinson and Finar, *J.*, 1946, 115.
[2] Albert and Gledhill, *Pharm. J.*, 1945, **154**, 127.
[3] Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169.
[4] Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **26**, 160.

The pK_a values were determined by a method similar to that of Albert and Goldacre (*J.*, 1943, 454). As Albert and his colleagues made an allowance of +0·5 unit for the effect of the 50% alcohol used as solvent (see also Mizutani, *Z. physikal. Chem.*, 1925, **118**, 327), a similar correction was added to our figures so as to obtain a fair basis for comparison.

The high melting point, the relatively low pK_a value in comparison with those of its isomers, and its low solubility in alcohol suggest that the 1-fluoro-compound exists in a fairly high degree of association.

The examination of the fluoro-compounds for bacteriostatic activity is not yet complete and a summary of the results will appear in a further communication. Results so far obtained indicate that the compounds of this group are powerful bacteriostatic agents, thus supporting the hypothesis of Albert, Rubbo, *et al.* (*loc. cit.*) that, in the acridine series, a pK_a value greater than 7·0 is an essential requirement for powerful antibacterial activity.

Acetyl Derivatives.—The fluoro-5-aminoacridines formed mono- and di-acetyl derivatives under similar conditions to those employed for the chloro-compounds (Wilkinson and Finar, *loc. cit.*). All exhibited fluorescence in ultra-violet light both in the solid state and in alcoholic solution. In general, the properties of both mono- and di-acetyl derivatives resembled those of their chlorine analogues.

Quaternary Salts.—A number of quaternary salts were prepared by the methods of Albert and Ritchie (*J.*, 1943, 458) and, of these, the antibacterial activity of *2-fluoro-5-amino-10-methylacridinium bromide* is being compared with that of the corresponding *2-chloro*-compound.

Experimental.

(M. p.'s are corrected unless over 300°).

m- *and* p-*Fluoroaniline.*—*m*- or *p*-Nitrobenzenediazonium borofluoride (Balz and Schiemann, *loc. cit.*) was decomposed in 10 g. portions by cautious direct heating, and the fluoronitrobenzene isolated from the residue and distillate by steam distillation. *m*-Fluoronitrobenzene had b. p. 198—200°/760 mm. (Swarts, *Rec. Trav. chim.*, 1913, **32**, 60, gives b. p. 200°/756 mm.). *p*-Fluoronitrobenzene had b. p. 203—205°/745 mm. (Swarts, *ibid.*, 1914, **33**, 265, gives b. p. 205°/735 mm.).

Each fluoronitrobenzene was reduced catalytically by hydrogenation in methanol (5 vols.) under 5 atms. pressure at 20° in the presence of 3% Adams's platinum oxide. The theoretical amount of hydrogen was absorbed. Solvent was removed, and the residue dissolved in warm 2N-hydrochloric acid and extracted with benzene to remove any non-basic impurities. Excess of 50% sodium hydroxide was added to regenerate the base, which was extracted with ether. The extract was dried (KOH), the

solvent removed, and the product distilled. *m*-Fluoroaniline was obtained in 90% yield, b. p. 185—187°/770 mm. (Swarts, *Bull. Acad. roy. Belg.*, 1912, 481, gives b. p. 186°/754 mm.). *p*-Fluoroaniline (yield 91%) had b. p. 187—188°/762 mm. (Swarts, *loc. cit.*, gives b. p. 187°/753 mm.).

o-Bromofluorobenzene was prepared according to the method of Bergmann, Engel, and Sándor (*Z. physikal. Chem.*, 1930, **10**, 106). Our product had b. p. 44°/11 mm. (lit., 57°/22 mm.).

Preparation of Fluorodiphenylamine-2-carboxylic Acids.—(a) *From* m- *and* p-*fluoroanilines.* The appropriate fluoroaniline (7·9 g.) and copper-bronze catalyst (0·5 g.) were refluxed with a solution of *o*-iodobenzoic acid (12·45 g.) and potassium carbonate (7 g.) in water (50 c.c.) for 3 hours. The excess of fluoroaniline was removed by steam distillation and the liquid filtered. Ammonium chloride solution (30% *w*/*v*, 50 c.c.) was added to precipitate the product as ammonium salt. This was dissolved in N-sodium hydroxide (50 c.c.) and the free acid liberated by treatment with hydrochloric acid. *3'-Fluorodiphenylamine-2-carboxylic acid* (7·5 g., 64%) crystallised from 90% alcohol in light fawn rhombic plates, m. p. 164° (Found: C, 67·6; H, 4·5; N, 6·2. $C_{13}H_{10}O_2NF$ requires C, 67·6; H, 4·3; N, 6·05%). *4'-Fluorodiphenylamine-2-carboxylic acid* (9·3 g., 81%) crystallised from benzene in colourless hexagonal plates, m. p. 200° (Found: C, 67·6; H, 4·3; N, 6·1%).

(b) *From* o-*bromofluorobenzene.* Anthranilic acid (2·74 g., 0·02 mol.) was dissolved in *cyclo*hexanol (14 c.c.) and treated with anhydrous potassium carbonate (2·8 g., 0·04 equiv.). The solution was heated to boiling and allowed to cool to obtain the potassium salt in a voluminous form, a procedure since recommended by Goldberg and Kelly (*loc. cit.*). *o*-Bromofluorobenzene (3·5 g., 2·25 c.c., 0·02 mol.) and cuprous chloride (1 g.) were added and the mixture was refluxed for 8 hours. *cyclo*Hexanol was removed by steam distillation and the liquid filtered. The filtrate was concentrated to about 15 c.c. and treated with ammonium chloride solution (30% *w*/*v*, 20 c.c.). The precipitated ammonium salt was converted into the free acid as in (a) above. *2'-Fluorodiphenylamine-2-carboxylic acid* (yield, 2·47 g., 52%) crystallised from benzene in colourless plates, m. p. 186° (Found: C, 67·8; H, 4·7; N, 5·9%).

(c) *5-Fluorodiphenylamine-2-carboxylic acid.* 2-Chloro-4-fluorobenzoic acid (Magidson and Trawin, *loc. cit.*) (0·5 g.) was dissolved in hot amyl alcohol (5 c.c.) and the solution treated with anhydrous potassium carbonate (0·4 g.). When evolution of carbon dioxide ceased, aniline (0·4 g., 40% excess) and copper-bronze catalyst (0·1 g.) were added and the mixture was refluxed for 3½ hours. Aniline and amyl alcohol were removed by steam distillation and the liquid was filtered. The filtrate was acidified with 2N-hydrochloric acid to precipitate the product. The ammonium salt could not be isolated by addition of ammonium chloride. The *acid* crystallised from benzene in colourless needles, m. p. 183°. Admixture with 2-chloro-4-fluorobenzoic acid caused a depression of 25° (Found: C, 67·9; H, 4·8; N, 6·3%).

Preparation of 5-Chloroacridines.—(a) *5-Chloro-1-* and *-3-fluoroacridines.* The corresponding fluorodiphenylamine-2-carboxylic acid (1 g.) was refluxed for 45 minutes with phosphoryl chloride (4 c.c.) after which most of the excess of the latter was removed under reduced pressure. The residue was dissolved in chloroform (15 c.c.) and the solution treated with excess of ammonia cooled with ice. The chloroform layer was separated and the solvent removed; the yield was practically quantitative. *5-Chloro-1-fluoroacridine* crystallised from anhydrous benzene–light petroleum (b. p. 80—100°) in pale yellow needles, m. p. 142°. Partial hydrolysis to the corresponding acridone occurred when the solvents were not specially dried (Found: N, 6·1. $C_{13}H_7NClF$ requires N, 6·05%). *5-Chloro-3-fluoroacridine* crystallised from a mixture of 90 parts of alcohol and 10 parts of 2N-ammonia in colourless plates, which slowly turned brown on prolonged exposure to the air, m. p. 137° (Found: N, 6·1%).

(b) *5-Chloro-2- and -4-fluoroacridines.* 3'-Fluorodiphenylamine-2-carboxylic acid (15 g.) underwent ring closure as in (a). The crude mixture of 5-chloroacridines (15 g.) was dissolved in a hot mixture (250 c.c.) of 90 parts of alcohol and 10 parts of ammonia (*d* 0·88). The solution was cooled to 15° and the solid which crystallised (9·1 g., 60%) collected and recrystallised from 90% alcoholic ammonia, then from 80% alcoholic ammonia. The *acridine* was obtained in pale yellow needles, m. p. 151°, identical with the product obtained by ring closure of 5-fluorodiphenylamine-2-carboxylic acid (Found: N, 6·2%). Excess of water was added to the mother liquors to precipitate 5-chloro-4-fluoroacridine. Repetition of this treatment followed by repeated crystallisation from 40% alcoholic ammonia gave a substance, m. p. 106°. This was highly soluble in all the common organic solvents, but as a mixed m. p. with 5-chloro-2-fluoroacridine invariably showed a rise whatever proportions were admixed, it was concluded that it was a eutectic mixture of the two isomers (Found: N, 6·2%).

Preparation of 5-Aminoacridines.—The 5-chlorofluoroacridine (6·95 g., 0·03 mol.) was dissolved in phenol (20 g.) at 70—75°; finely powdered ammonium carbonate (2 g.) was added as rapidly as practicable and the temperature raised to 120° for 1 hour, with constant stirring throughout. Acetone (100 c.c.) was added to the cooled reaction mixture to precipitate the hydrochloride of the product, from which the base was obtained by treatment with sodium hydroxide.

1-Fluoro-5-aminoacridine (yield, 3·50 g., 55%) crystallised from chlorobenzene in bright yellow prisms, sparingly soluble in alcohol and benzene but readily soluble in acetic acid, m. p. 307° (corr.) (Found: C, 72·9; H, 4·1; N, 13·3. $C_{13}H_9N_2F$ requires C, 73·4; H, 4·25; N, 13·2%). The *hydrochloride monohydrate* crystallised in lemon-yellow prisms, m. p. > 360°, soluble in about 180 parts of water (Found: N, 10·7; loss at 130°/15 mm., 6·9. $C_{13}H_9N_2F,HCl,H_2O$ requires N, 10·5; H_2O, 6·75%).

2-Fluoro-5-aminoacridine (yield, 4·05 g., 64%) crystallised from 50% alcohol in bright yellow elongated prisms, m. p. 276° (Found: C, 73·0; H, 4·4; N, 13·2%). The *hydrochloride hemihydrate*, which was soluble in 500 parts of water, crystallised from 90% alcohol in lemon-yellow prisms, m. p. *ca.* 345° (decomp., with charring at about 320°) (Found: C, 60·6; H, 4·5; N, 10·9; loss at 130°/18 mm., 3·6. $C_{13}H_9N_2F,HCl,\frac{1}{2}H_2O$ requires C, 60·6; H, 4·3; N, 10·9; H_2O, 3·6%).

3-Fluoro-5-aminoacridine (yield, 4·35 g., 68%), crystallised from chlorobenzene in bright yellow elongated prisms, soluble in alcohol, m. p. 280° (Found: C, 73·5; H, 4·2; N, 13·2%). The *hydrochloride monohydrate* crystallised from 90% alcohol in lemon-yellow rectangular prisms, soluble in 1000 parts of water, m. p. 358° (decomp., with charring at about 340°) (Found: N, 10·5; loss at 130°/15 mm., 6·5%).

Separation of 2- and 4-Fluoro-5-aminoacridines.—The mixture of 5-chloro-2- and -4-fluoroacridines resulting from the ring closure of 3'-fluorodiphenylamine-2-carboxylic acid was converted into a mixture

of the corresponding 5-aminoacridines. The mixed hydrochlorides (3·0 g.) were extracted with water (45 c.c.); the mixture was cooled to *ca.* 10° and filtered. The residue (1·55 g.) consisted almost entirely of the hydrochloride of the 2-fluoro-isomer. The filtrate was made alkaline with 2N-sodium hydroxide to precipitate *4-fluoro-5-aminoacridine* (1·12 g.) which was purified by conversion into its hydrochloride and extraction with water (30 c.c.). The filtered aqueous extract on treatment with alkali gave the base (0·93 g.), m. p. 263—265°. Admixture with pure 2-fluoro-5-aminoacridine produced a depression of 2°. 4-Fluoro-5-aminoacridine crystallised from absolute alcohol in deep yellow prisms (Found: C, 73·4; H, 4·3; N, 13·2%), readily soluble in alcohol, m. p. 266°, depressed to 264° by admixture with its isomer. The *hydrochloride* crystallised from 90% alcohol in lemon-yellow prisms, soluble in about 35 parts of water and highly soluble in alcohol, m. p. 346° (decomp. with charring at *ca.* 320°) (Found: N, 11·1. $C_{13}H_9N_2F,HCl$ requires N, 11·25%).

With the exception of the 2-fluoro-isomer, all the bases exhibited a faint green fluorescence in ultra-violet light in the solid state, whilst under similar conditions alcoholic solutions of all four showed a vivid light blue fluorescence unaffected by the presence of acid or alkali. Dilute solutions of bases and hydrochlorides exhibited an intense blue fluorescence by daylight.

Acetyl Derivatives.—The mono- and di-acetyl derivatives were prepared by methods similar to those used for the chlorine analogues (*J.*, 1946, 115). The base (1 g.) was heated at 105° for 30 minutes with acetic anhydride (3 c.c.) and the cooled mixture treated with water. After neutralisation with ammonia, the monoacetyl derivatives were collected (yield about 90%).

1-Fluoro-5-acetamidoacridine crystallised from 70% alcohol in cream-white needles, m. p. 272° (Found: N, 10·9. $C_{15}H_{11}ON_2F$ requires N, 11·0%). *2-Fluoro-5-acetamidoacridine* crystallised from 50% alcohol in fine colourless needles, m. p. 273° (with some preliminary charring) (Found: N, 10·85%). *3-Fluoro-5-acetamidoacridine* crystallised from 60% alcohol in cream-white silky needles, m. p. 292° (Found: N, 10·8%). *4-Fluoro-5-acetamidoacridine* crystallised from 70% alcohol in pale yellow needles, m. p. 264° (with some preliminary charring) (Found: N, 10·9%).

The diacetyl derivatives were prepared by refluxing the base (1 g.) with acetic anhydride (4 c.c.) for 30 minutes, the products being isolated in the same manner as the monoacetyl derivatives.

1-Fluoro-5-diacetylaminoacridine was obtained in cream white hexagonal plates, m. p. 193°, from absolute alcohol (Found: N, 9·3. $C_{17}H_{13}O_2N_2F$ requires N, 9·45%). *2-Fluoro-5-diacetylaminoacridine* crystallised from 60% alcohol in colourless rhombic plates, m. p. 178—179°. (Found: N, 9·6%). *3-Fluoro-5-diacetylaminoacridine* crystallised from 60% alcohol in highly refractive colourless needles, m. p. 173° (Found: N, 9·6%). *4-Fluoro-5-diacetylaminoacridine* crystallised from 60% alcohol in coloulress refractive rhombs, m. p. 171—172° (Found: N, 9·6%).

In the solid state, both series of acetyl derivatives resembled the chlorine compounds in exhibiting a blue fluorescence under ultra-violet light, but that of the fluorine compounds was less vivid. In alcoholic solution under the same conditions, both series fluoresced blue or violet, the fluorescence being discharged or considerably diminished by acid, but turned to a vivid green by alkali. None exhibited fluorescence by daylight.

Like the chlorine and methyl analogues, the fluorinated acetyl derivatives showed evidence of their basic nature by the deep yellow colour of their solutions in mineral acids.

Quaternary Salts.—2-Fluoro-5-acetamidoacridine (0·4 g.) was heated with methyl toluene-*p*-sulphonate (0·4 g.) in nitrobenzene (4 c.c.) at 180° for 30 minutes, according to the method of Albert and Ritchie (*loc. cit.*). Benzene (10 c.c.) was added to the cooled mixture, and, after 24 hours, the solid was separated by decantation, dissolved in water (5 c.c.), and hydrolysed by heating on a steam-bath for 15 minutes with hydrobromic acid (50%, 2 c.c.). *2-Fluoro-5-amino-10-methylacridinium bromide*, which separated on cooling (0·4 g.), crystallised from water, in which it was readily soluble, in deep yellow irregular prisms, m. p. 300° (decomp.) (Found: N, 9·1. $C_{14}H_{12}N_2BrF$ requires N, 9·1%). An attempt to prepare the 3-fluoro-isomer by the same method led to the production of a considerable amount of tar, but the corresponding iodide was prepared by the alternative procedure also described by Albert and Ritchie (*loc. cit.*). 3-Fluoro-5-aminoacridine (1 g.) was refluxed for 4 hours with methanol (4 c.c.) and methyl iodide (2·5 g.). The solid (1·25 g.) was filtered off and refluxed for 20 minutes with acetone (20 c.c.) to remove the red impurity, presumably methylated in the 5-position. The product gave no precipitate when an aqueous solution was treated with N-sodium hydrogen carbonate. *3-Fluoro-5-amino-10-methylacridinium iodide* crystallised from water in bright yellow prisms, m. p. 288° (decomp.) (Found: N, 7·9. $C_{14}H_{12}N_2IF$ requires N, 7·9%).

The following new chlorine derivatives were prepared for comparison by the first method. *2-Chloro-5-amino-10-methylacridinium bromide* crystallised from water in bright yellow prisms, m. p. 319° (decomp.) (Found: N, 8·7. $C_{14}H_{12}N_2ClBr$ requires N, 8·65%). *3-Chloro-5-amino-10-methylacridinium bromide* crystallised from water in small bright yellow irregular prisms, m. p. 312—314° (decomp.) (Found: N, 8·5%).

Determination of Dissociation Constants.—The fluoroaminoacridine (0·00025 g.-mol.) was dissolved in neutral 50% alcohol (*ca.* 40—50 c.c.) at 20° in a beaker provided with a compressed air stirrer. Glass and calomel electrodes were connected by means of screened leads to a Cambridge pH meter, standardised against buffer solutions of pH 3·97, 6·20, 8·00, and 9·00. The solution was titrated with 0·5N-hydrochloric acid from a microburette, the readings being plotted against the pH, and the pK_a value read off from the resulting curve.

The authors wish to thank Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, and Dr. H. J. Barber and the Directors of May and Baker Ltd. for facilities kindly placed at the disposal of one of them (J. H. W.).

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[*Received, September 17th*, 1946.]

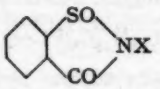
146. *The Formation of Some Benz-1 : 3-thiazine Derivatives by the Reduction of Benzisothiazolones.*

By Jack S. Ingram and (the late) Ernest W. McClelland.

2-Methyl-, 2-ethyl-, and 2-benzyl-dihydro-1 : 3-benzthiazine-4-ones are formed when the *N*-acetyl, -propionyl, and -phenylacetyl derivatives respectively of dihydrobenz*iso*thiazolone or their *S*-oxides are reduced with zinc and acid, the change involving an expansion of the hetero-ring. The corresponding 2-phenyl compound is not obtainable by the similar reduction of the *N*-benzoyldihydrobenz*iso*thiazolone but it is readily produced by condensation of benzaldehyde with 2 : 2′-dithiobenzamide. The properties and reactions of these substances have been examined.

In the course of a study of some derivatives of benz*iso*thiazolone (Hart, McClelland, and Fowkes, *J.*, 1938, 2214; Bartlett, Hart, and McClelland, *J.*, 1939, 760) the observation was made by Hart that *N*-acetylbenz*iso*thiazolone *S*-oxide (I; X = COMe) was converted on reduction into the benz-*m*-thiazine derivative (II). The present paper records a further examination of such reactions and the substances which result.

The reduction products of the *iso*thiazole oxides of type (I) vary according to the nature of the *N*-substituent, X. Thus the benzenesulphonyl and the benzoyl derivative (I;



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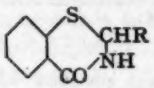

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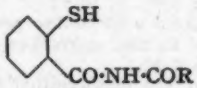
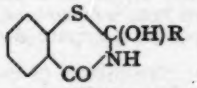


(III.)

X = SO_2Ph or COPh) yield the corresponding disulphides $(-S\cdot C_6H_4\cdot CO\cdot NHX)_2$, together with 2 : 2′-dithiobenzamide in the latter case. When, however, the *N*-substituent is an acyl group (X = COR, where R = Me, Et, CH_2Ph) ring expansion takes place with formation of the corresponding dihydrothiazine (II). The formation of the thiazines is evidently by way of the thiazolones, since the latter also give the thiazines on reduction under similar conditions. Reduction of the thiazolone presumably first yields the mercaptoamide (III), which passes into



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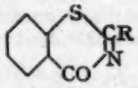

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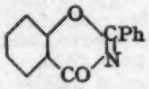

(VI.)

the final product by the reduction of either the internal self-addition compound (IV) or the condensation product (V). The intermediate (V), which has not in fact been isolated, would be closely analogous to Titherley's 2-phenyl-1 : 3-benzoxazine-4-one (VI) (*J.*, 1910, **97**, 200).

Although reduction of the *N*-benzoylbenz*iso*thiazolone (I, X = COPh) yielded none of the expected phenyldihydro-1 : 3-benzthiazine-4-one, this substance was readily obtained by condensation of 2 : 2′-dithiobenzamide with benzaldehyde, no additional reduction being found necessary. No corresponding reaction was found using acetaldehyde in place of benzaldehyde.

The behaviour of these dihydrobenz-1 : 3-thiazine derivatives has been studied. In view of the close structural relationship between the benz*iso*thiazolones and the benz-1 : 3-thiazine-4-ones into which they are converted, it was of interest to find whether they would show analogous reactions. The former substances are transformed by heating with potassium acetate and acetic anhydride into thionaphthen derivatives, the group NX being eliminated (McClelland, *J.*, 1929, 1588; McClelland and D'Silva, *J.*, 1931, 2972; 1932, 2883; Bartlett and McClelland, *J.*, 1934, 818), and on the other hand they are readily oxidised to substances of the saccharin type. The benzthiazine-4-ones, however, are merely acetylated by acetic anhydride and potassium acetate and no rupture of the ring occurs. Oxidation by hydrogen peroxide yields a soluble acidic substance which is probably *o*-sulphobenzoic acid, but only on one occasion was there any indication of the production of a trace of a saccharin. When the *N*-acyl derivatives are oxidised the S-*dioxide* of the parent thiazine is obtained, but attempts to convert this into a saccharin by heating with pyridine or alkali were unsuccessful.

Experimental.

Preparation of the Acyldihydrobenzisothiazolone S-*Oxides*.—The method used by Hart, McClelland, and Fowkes (*loc. cit.*) to prepare the 1-acetyl compound, applied to propionamide yielded 2-*keto*-1-*propionyl*-1 : 2-*dihydrobenzisothiazole* S-*oxide*, crystallising in colourless needles, m. p. 136°, from alcohol (charcoal)

(Found: C, 53·6; H, 4·1; S, 14·2. $C_{10}H_9O_3NS$ requires C, 53·8; H, 4·0; S, 14·4%). Similarly, phenylacetamide gave 2-*keto*-1-*phenylacetyl*-1 : 2-*dihydrobenzisothiazole* S-*oxide*, crystallising in colourless prisms, m. p. 162° (Found: C, 63·0; H, 3·9; S, 11·4. $C_{15}H_{11}O_3NS$ requires C, 63·2; H, 3·9; S, 11·2%), and benzamide yielded 2-*keto*-1-*benzoyl*-1 : 2-*dihydrobenzisothiazole* S-*oxide* as fine colourless needles from benzene, m. p. 150° (Found: C, 62·4; H, 3·6; N, 5·1. $C_{14}H_9O_3NS$ requires C, 62·0; H, 3·3; N, 5·2%).

Reduction of 2-*Keto*-1-*benzoyl*-1 : 2-*dihydrobenzisothiazole* S-*Oxide*.—The benz*iso*thiazolone oxide (2 g.) was boiled for 4 hrs. in glacial acetic acid (40 c.c.) with hydrochloric acid (3 c.c.) and zinc dust (2 g.). The filtered solution gave, on dilution with water, a white precipitate having a thiophenolic odour and giving a transient green colour with ferric chloride. It was soluble in alkali and was oxidised by iodine in alcohol to *NN'*-dibenzoyl-2 : 2'-dithiobenzamide, m. p. 189° (compare Reissert and Manus, *Ber.*, 1928, **61**, 1308).

Reduction of 2-*Keto*-1-*acetyl*-1 : 2-*dihydrobenzisothiazole* S-*Oxide*.—This substance was not affected by sulphur dioxide in boiling alcohol, but was readily reduced by zinc dust as follows: the benz*iso*thiazolone *S*-oxide (20 g.) was boiled in glacial acetic acid (275 c.c.) with concentrated hydrochloric acid (30 c.c.) and zinc dust (30 g.) for 4 hours with stirring. The solution, filtered from excess of zinc, was poured into water (800 c.c.). The precipitate was collected and further quantities were obtained by alternately concentrating and diluting the mother-liquor several times. The product was recrystallised from alcohol (yield 13·5 g.). 2-*Methyldihydro*-1 : 3-*benzthiazine*-4-*one* was thus obtained as colourless needles, m. p. 175° (Found: C, 60·0, 60·4; H, 5·0, 5·3; S, 17·9. C_9H_9ONS requires C, 60·3; H, 5·0; S, 17·9%). When larger quantities of hydrochloric acid were used the yield was much less and 2 : 2'-dithiobenzamide, m. p. 250°, and 2 : 2'-dithiobenzoic acid, m. p. 289°, were also produced. The N-*acetyl* derivative formed colourless needles from alcohol, m. p. 70° (Found: C, 60·0; H, 5·2; S, 16·6. $C_{11}H_{11}O_2NS$ requires C, 59·7; H, 5·0; S, 16·5%). This substance was volatile in steam, and was hydrolysed by boiling dilute hydrochloric acid to the parent compound. The N-*benzoyl* derivative, prepared by benzoylation in pyridine, formed colourless needles, m. p. 127° (Found: C, 67·9; H, 4·9. $C_{16}H_{13}O_2NS$ requires C, 67·9; H, 4·6%).

When the methyldihydrobenzthiazinone was distilled with dilute aqueous sodium hydroxide, acetaldehyde was found in quantity in the distillate, and addition of ferric chloride to the acidified reaction mixture yielded 2 : 2'-dithiobenzoic acid. Oxidation of the methylbenzthiazinone with hydrogen peroxide in glacial acetic acid at 100° gave a water-soluble, hygroscopic, yellow, strongly acidic substance and a sweet taste was sometimes detected.

Oxidation of the acetyl or the benzoyl derivative by hydrogen peroxide in aqueous suspension at 100° yielded the S-*dioxide* of the parent substance, crystallising from water (charcoal) in colourless needles, m. p. 163° (Found: C, 51·0; H, 4·1; S, 15·1. $C_9H_9O_3NS$ requires C, 51·2; H, 4·3; S, 15·2%), together with hygroscopic material as produced in the previous oxidation.

Attempts at direct methylation of the methyldihydrobenzthiazinone with methyl iodide, methyl sulphate, or diazomethane were unsuccessful. When the substance was heated in a sealed tube at 120—130° with methyl iodide, methyl alcohol, and potassium carbonate, gas was evolved, a smell of iodoform was observed, and 2-methylthiobenzamide, m. p. 150°, was produced (compare McClelland and Warren, *J.*, 1929, 2625).

Preparation of 2-*Ethyl- and* 2-*Benzyl-dihydro*-1 : 3-*benzthiazine*-4-*ones*.—Reduction in the same way converted the 1-propionyl- and 1-phenylacetyl-2-ketodihydrobenz*iso*thiazole *S*-oxides into 2-*ethyldihydro*-1 : 3-*benzthiazine*-4-*one*, colourless needles from alcohol, m. p. 112° (Found: C, 62·1; H, 5·5; S, 16·9. $C_{10}H_{11}ONS$ requires C, 62·2; H, 5·7; S, 16·6%), giving the acetyl derivative as an oil, and 2-*benzyldihydro*-1 : 3-*benzthiazine*-4-*one*, colourless needles from alcohol, m. p. 149·5° (Found: C, 70·7; H, 4·8; S, 12·5. $C_{15}H_{13}ONS$ requires C, 70·6; H, 5·1; S, 12·2%). These substances are insoluble in alkali and give no reaction with ferric chloride.

Reduction of the Benzisothiazolones.—When the acyl and benzoyl thiazolones were reduced instead of their *S*-oxides the products were respectively the same.

Preparation of 2-*Phenyldihydro*-1 : 3-*benzthiazine*-4-*one*.—2 : 2'-Dithiobenzamide (5 g.) was heated with benzaldehyde (10 c.c.) and potassium acetate (fused, 8 g.) at 160° for 3 hours. The pale yellow mass when cold was ground up, and the excess of benzaldehyde removed in a current of steam or by washing with aqueous alcohol. The residue, crystallised from alcohol in colourless needles, m. p. 176° (yield 4·5 g.), was 2-*phenyldihydro*-1 : 3-*benzthiazine*-4-*one* (Found: C, 69·6; H, 4·6; S, 6·1; *M*, in benzene, 247. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6; S, 5·8%; *M*, 241). It is sparingly soluble in water, insoluble in alkali, and gives no reaction for a disulphide and no colouration with ferric chloride.

KING'S COLLEGE, LONDON. [*Received, September 17th*, 1946.]

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147. *Oxidations and Dehydrogenations with Selenium Dioxide.*

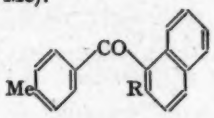
By G. M. BADGER.

1-*p*-Toluoyl-2-methylnaphthalene (I, R = Me) has been oxidised with selenium dioxide to 1-p-*toluoylnaphthalene*-2-*carboxylic acid* (I, R = CO_2H), the constitution of which has been proved by conversion into 6-methyl-1 : 2-benzanthraquinone. Some experiments on the use of selenium dioxide as a dehydrogenating agent for hydroaromatic compounds are also reported.

SELENIUM dioxide was first introduced as an oxidising agent by Riley (B.P. 354,798; Riley, Morley, and Friend, *J.*, 1932, 1875). It is now finding considerable application in the preparation of compounds which are either unobtainable, or obtained only with difficulty, using

other oxidising agents. (For a comprehensive review see Waitkins and Clark, *Chem. Reviews*, 1945, **36**, 235.)

A particularly useful property of selenium dioxide is its power to oxidise activated methylene or methyl groups. Cook (*J.*, 1932, 1472; 1933, 1592) prepared 2-carboxy-1 : 1′-dinaphthyl ketone from 2-methyl-1 : 1′-dinaphthyl ketone, and oxidised 1-α-naphthoyl-2 : 6-dimethylnaphthalene to a mono-aldehyde, the constitution of which was not proved, although it was considered probable that the methyl group adjacent to the carbonyl group had been oxidised. It was therefore of interest to attempt the oxidation of 1-*p*-toluoyl-2-methylnaphthalene (I, R = Me).



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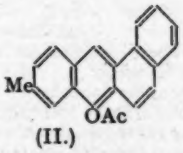

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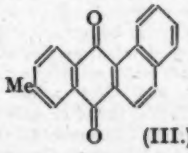

(III.)

In aqueous suspension at 230°, selenium dioxide oxidised this ketone to 1-p-*toluoylnaphthalene-2-carboxylic acid* (I, R = CO_2H), which was purified *via* the *acetoxy-lactone*. Attempts to ring-close this acid to 6-methyl-1 : 2-benzanthraquinone (III) using benzoyl chloride with a trace of sulphuric acid (Badger and Cook, *J.*, 1939, 802), or with concentrated sulphuric acid at 100°, were unsuccessful. The keto-acid was, however, reduced with zinc and sodium hydroxide to 1-p-*methylbenzylnaphthalene-2-carboxylic acid*, which was smoothly converted into 10-*acetoxy*-6-*methyl*-1 : 2-*benzanthracene* (II) with zinc chloride in acetic anhydride–acetic acid (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 1032). The constitution was finally confirmed by oxidation of this derivative to 6-methyl-1 : 2-benzanthraquinone (III), and the synthesis therefore provides an alternative route to derivatives of the carcinogenic hydrocarbon, 6-methyl-1 : 2-benzanthracene. It is of interest that Cook (*loc. cit.*) was unable to oxidise the methyl group of 6-methyl-1 : 2-benzanthraquinone with selenium dioxide.

The efficiency of selenium dioxide as an oxidising agent appears to depend on the degree of activation of the group to be oxidised and on the temperature of reaction. This is illustrated by the fact that 9 : 10-dihydroanthracene was smoothly dehydrogenated to anthracene in boiling acetic acid, but not in alcohol, while at high temperatures anthracene was oxidised to anthraquinone. Under the same conditions phenanthrene gave no phenanthraquinone (compare Astin, Moulds, and Riley, *J.*, 1935, 901; Postowsky and Lugowkin, *Ber.*, 1935, **68**, 852). Attempts to dehydrogenate *s*-octahydroanthracene and *as*-octahydroanthracene in boiling alcohol or acetic acid were, however, unsuccessful. In aqueous suspension at 150°, with the theoretical quantity of selenium dioxide required for dehydrogenation, but not oxidation, both octahydroanthracenes gave mixtures of anthraquinone and unchanged material. In the octahydroanthracenes the hydrogen atoms are not highly activated, and the temperature required for dehydrogenation would appear to be almost identical with that required for oxidation. Hexahydropyrene (Cameron, Cook, and Graham, *J.*, 1945, 286) was dehydrogenated to pyrene in acetic acid, although a dark product was also formed.

Experimental.

1-p-*Toluoylnaphthalene-2-carboxylic Acid* (I, R = CO_2H).—A mixture of 1-*p*-toluoyl-2-methylnaphthalene (I, R = Me) (4 g.), selenium dioxide (7 g.), and water (7 c.c.) was heated in a sealed tube at 230—240° for 4 hours. The solid was extracted with hot sodium carbonate, and the crude acid precipitated with hydrochloric acid. After recrystallisation from acetic acid it formed colourless prisms, m. p. 215—218°. (Yield, 11 g. from 6 such experiments, with 5 g. ketone recovered unchanged.) The *acetoxy-lactone*, prepared by heating the acid (2 g.) with pyridine (12 c.c.) and acetic anhydride (4 c.c.) for 2 hours on the steam-bath, recrystallised from alcohol and formed colourless transparent needles, m. p. 145—147° (Found : C, 75·6; H, 5·0. $C_{21}H_{14}O_4$ requires C, 75·9; H, 4·8%). Pure 1-p-*toluoylnaphthalene-2-carboxylic acid*, recovered after hydrolysis of the acetoxy-lactone with potassium hydroxide, formed colourless transparent prisms from acetic acid, m. p. 220—222° (Found : C, 78·25; H, 5·0. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%).

Attempts to ring-close this acid with concentrated sulphuric acid at 100° for 3 hours, or with benzoyl chloride and a trace of sulphuric acid at 130°, were unsuccessful.

1-p-*Methylbenzylnaphthalene-2-carboxylic Acid*.—A mixture of the above acid (8·5 g.), sodium hydroxide (12 g.), zinc dust (12 g.), and water (130 c.c.) was boiled under reflux for 24 hours. After filtration, the *acid* was precipitated with hydrochloric acid, and recrystallised from 80% acetic acid. It formed colourless crystals (3·5 g.), m. p. 188—190° (Found : C, 82·3; H, 5·9. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

10-*Acetoxy*-6-*methyl*-1 : 2-*benzanthracene*.—A mixture of the above acid (1 g.), acetic acid (6 c.c.), acetic anhydride (4 c.c.), and zinc chloride (0·1 g.) was refluxed for 1 hour. Water was added and the precipitated product collected and recrystallised from acetic acid. The *benzanthracene* (0·65 g.) formed

pale yellow prisms, m. p. 174·5—176° (Found: C, 84·3; H, 5·35. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·3%).

6-Methyl-1 : 2-benzanthraquinone.—10-Acetoxy-6-methyl-1 : 2-benzanthracene (0·1 g.) was boiled under reflux for ½ hour with sodium dichromate (0·5 g.) in acetic acid (5 c.c.). The product, recrystallised from glacial acetic acid, formed yellow needles, m. p. 176—177° (corr.) alone, or mixed with authentic 6-methyl-1 : 2-benzanthraquinone.

Action of Selenium Dioxide on Hydroanthracenes.—A solution of 9 : 10-dihydroanthracene (1 g.), selenium dioxide (2 g.), water (2 c.c.), and acetic acid (50 c.c.) was refluxed for 1½ hours. The filtered solution was poured into water, and the solid collected and recrystallised from alcohol. It formed almost colourless plates (0·6 g.), m. p. 214—215°, alone or mixed with anthracene. The dehydrogenation was not effected by refluxing for a similar time in alcohol.

Similar experiments with *s*-octahydroanthracene and *as*-octahydroanthracene, gave very dark mixtures from which only the unchanged octahydroanthracenes could be isolated.

Action of Selenium Dioxide on Anthracene.—Anthracene (2 g.) was heated in a sealed tube at 220—230° for 3 hours with selenium dioxide (4 g.) and water (4 c.c.). The product, recrystallised from acetic acid, had m. p. 284—285°, alone or mixed with anthraquinone. Yield, 1·62 g.

No phenanthraquinone could be isolated from a similar experiment with phenanthrene.

Action of Selenium Dioxide on Hexahydropyrene.—A solution of hexahydropyrene (1 g.), selenium dioxide (4 g.), water (4 c.c.), and acetic acid (50 c.c.) was refluxed for 50 minutes. The product, purified from dark impurities through the sparingly soluble picrate, had m. p. 148—150°, alone or mixed with authentic pyrene. Yield, 0·3 g.

My thanks are due to Professor J. W. Cook, F.R.S., for his interest in this work, which was made possible by the award of an Imperial Chemical Industries Research Fellowship.

THE UNIVERSITY OF GLASGOW. [*Received, September 17th*, 1946.]

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148. *The Alkaline Fission of Some 2-Substituted Dimethylethylsulphonium Iodides.*

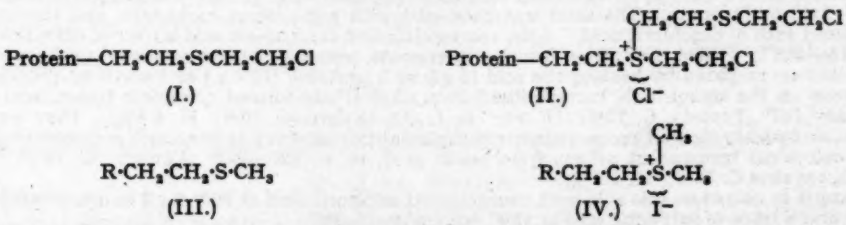
By C. W. CRANE and H. N. RYDON.

The action of alkali on five compounds of the general structure $R{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$ (R = Ph·CO·O, PhO, MeS, Ph·CO·NH, and Ph·CH_2·NH) has been investigated. The behaviour of the last three compounds is normal but the first two are remarkably sensitive to alkali and undergo " double elimination ", thus:

$$R{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^- \longrightarrow RH + CH{\equiv}CH + SMe_2 + HI$$

The theoretical basis of this novel reaction is discussed and its possible utility in synthetic and degradative work is pointed out.

THE work now described was stimulated by various observations (Northrop; du Vigneaud; Ball; private communications, 1942—1943) that the products of the action of " mustard gas " on proteins were more easily split by alkali than would be expected if they had the simple structure (I). It seemed to us that this alkali-lability might be due to the formation of sulphonium salts of the general type (II), and we accordingly carried out a number of experiments on model compounds of types (III) and (IV), corresponding to (I) and (II), respectively, in which R was Ph·CO·O, PhO, MeS, Ph·CO·NH, and Ph·CH_2·NH to simulate combination with carboxyl, phenolic hydroxyl, thiol, amide, and amino-groups in the protein molecule. The results of these



experiments seem of sufficient general interest to warrant publication, irrespective of whether they do or do not throw any light on the mode of action of " mustard gas."

Dimethyl-2-benzoyloxyethylsulphonium iodide (VI) was prepared as follows:

$$HO{\cdot}CH_2{\cdot}CH_2{\cdot}SMe \xrightarrow{Ph{\cdot}COCl} Ph{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}SMe \xrightarrow{MeI} Ph{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$$
(V.) (VI.)

It is remarkably easily decomposed in alkaline solution, liberating two equivalents of acid (one of benzoic acid, one of hydriodic). Under identical conditions (M/100-solution in 60% alcohol at 25° and pH 11) the sulphonium salt (VI) liberates 1 equiv. of acid in 4 mins. whereas the parent *methyl 2-benzoyloxyethyl sulphide* (V) shows no trace of hydrolysis in 9 hours. In aqueous solution the liberation of acid follows first-order kinetics; the following data relate to the liberation of the first equivalent of acid :

Rate of hydrolysis of (VI) *in aqueous solution at* 25°.

Initial concn. of (VI), M	0·01	0·02	0·02
pH (maintained constant)	10	10	11
k (min.$^{-1}$)	0·0089	0·0078	0·079
Time for 50% change (mins.)	77·6	88·6	8·8

Even at pH 7·4 and 37° slight hydrolysis occurs, 0·02 equiv. of acid being liberated under these conditions in 6 hours. Qualitative experiments, in which the sulphonium salt (VI) was boiled with 10% sodium hydroxide solution, resulted in the isolation or detection as reaction products of acetylene (detected qualitatively only), dimethyl sulphide (60% yield), and benzoic acid (100% yield), together with a little methyl iodide. Clearly the main reaction is the following unusual decomposition :

$$Ph{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^- + 2NaOH \longrightarrow Ph{\cdot}CO_2Na + CH{\vdots}CH + SMe_2 + NaI + 2H_2O$$

accompanied to a small extent by simple dissociation of the sulphonium iodide into the sulphide (V) and methyl iodide.

Dimethyl-2-phenoxyethylsulphonium iodide (VIII) was prepared as follows :

$$Cl{\cdot}\overset{\alpha}{C}H_2{\cdot}CH_2{\cdot}SMe \xrightarrow{PhONa} \underset{\text{(VII.)}}{PhO{\cdot}CH_2{\cdot}CH_2{\cdot}SMe} \xrightarrow{MeI} \underset{\text{(VIII.)}}{PhO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-}$$

Once again the sulphonium salt (VIII) is much more alkali-labile than the corresponding sulphide, *methyl 2-phenoxyethyl sulphide* (VII), the latter being quite unaffected by 5 minutes' boiling with 40% sodium hydroxide solution whereas the former is measurably and rapidly hydrolysed at 100°, even at pH 7·4. It will be seen from the details given on p. 770 that the rate of hydrolysis of (VIII) is markedly influenced by pH. The alkaline fission of (VIII) is rather less rapid than that of (VI), an M/100-solution of (VIII) being only 5% hydrolysed in 180 mins. at pH 10 and 25°, conditions under which (VI) is 25% hydrolysed in 78 mins. Nevertheless, the alkali-lability of (VIII) is quite remarkable, decomposition of M/100-solutions being complete within one minute at pH values of 10 or higher. Isolation experiments, in which (VIII) was boiled with 10% sodium hydroxide solution, showed that the main decomposition was into phenol (isolated in 85% yield), dimethyl sulphide (39% yield), and acetylene (detected qualitatively only), thus :

$$PhO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^- + 2NaOH \longrightarrow PhONa + CH{\vdots}CH + SMe_2 + NaI + 2H_2O$$

There was also about 10% of simple dissociation into methyl iodide and the sulphide (VII).

Dimethyl-2-methylthioethylsulphonium iodide (IX) was much less sensitive to alkali; no free thiol groups could be detected by iodometric titration when this compound was kept in M/100-solution at 25° and pH 10, 11, or 12 for periods up to 5½ hours. With boiling 10% sodium hydroxide traces of thiol compounds could be detected by the nitroprusside reaction in the early stages, but the principal reaction appeared to be fission to dimethyl and methyl vinyl sulphides, thus :

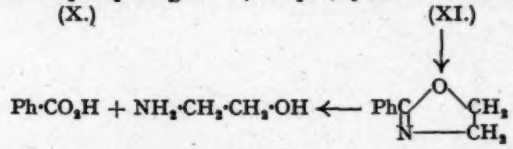
$$\underset{\text{(IX.)}}{SMe{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-} + NaOH \longrightarrow SMe{\cdot}CH{:}CH_2 + SMe_2 + NaI + H_2O$$

No acetylene could be detected in the reaction products; there was a little dissociation into methyl iodide and 1 : 2-bismethylthioethane.

Dimethyl-2-benzamidoethylsulphonium iodide (X), on being boiled with 10% sodium hydroxide gave, as the only isolated products, dimethyl sulphide (65% yield), 2-phenyl-4 : 5-dihydro-oxazole (XII) (43% yield), and benzoic acid (11% yield); monoethanolamine, although almost certainly present, could not be isolated; acetylene could not be detected. Since control experiments showed that (XII) is partly hydrolysed under our reaction conditions, it seems reasonable to represent the action of alkali on (X) as a simple elimination reaction followed by cyclisation

of the intermediate *N*-vinylbenzamide (XI) to the oxazoline (XII), which is then partly hydrolysed:

$$\underset{\text{(X.)}}{Ph\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^-} \longrightarrow Me_2S + \underset{\text{(XI.)}}{[Ph\cdot CO\cdot NH\cdot CH{:}CH_2]}$$



$$Ph\cdot CO_2H + NH_2\cdot CH_2\cdot CH_2\cdot OH \longleftarrow \text{(XII.)}$$

Dimethyl-2-benzylaminoethylsulphonium iodide (XIII) was very stable to alkali, no free amino-groups being liberated in M/100-solution at pH 12 even at 100°. With boiling 10% sodium hydroxide the decomposition was complex, the isolated reaction products being methyl vinyl sulphide, benzyldimethylamine, *methyl 2-benzylaminoethyl sulphide* (XIV) and *benzyldimethyl-(2-methylthioethyl)ammonium iodide* (XV); no acetylene was formed. Since the ammonium salt (XV), which may be prepared by the action of methyl iodide on the base (XIV) in alkaline solution, is partly split into methyl vinyl sulphide and benzyldimethylamine under our reaction conditions, the following is the probable course of the alkaline fission of (XIII):

(i) $$\underset{\text{(XIII.)}}{CH_2Ph\cdot NH\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^-} \longrightarrow \underset{\text{(XIV.)}}{CH_2Ph\cdot NH\cdot CH_2\cdot CH_2\cdot SMe} + MeI$$

(ii) $$\text{(XIV)} + 2MeI + NaOH \longrightarrow \underset{\text{(XV.)}}{CH_2Ph\cdot \overset{+}{N}Me_2\cdot CH_2\cdot CH_2\cdot SMe\}I^-} + NaI + H_2O$$

(iii) $$\text{(XV)} + NaOH \longrightarrow CH_2Ph\cdot NMe_2 + CH_2{:}CH\cdot SMe + NaI + H_2O$$

Clearly, the main initial reaction here is dissociation, followed by a number of secondary reactions.

Focusing attention on the initial changes, we may summarise our results by saying that the alkaline fission of the five β-substituted-ethyldimethylsulphonium iodides studied takes place by way of one or more of the following three reactions:

$$R\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- \begin{cases} \longrightarrow RH + CH{:}CH + SMe_2 + HI & (\text{"Double elimination"}) \\ \longrightarrow R\cdot CH{:}CH_2 + SMe_2 + HI & (\text{"Single elimination"}) \\ \longrightarrow R\cdot CH_2\cdot CH_2\cdot SMe + MeI & (\text{"Dissociation"}) \end{cases}$$

"Double elimination" predominates when R = Ph·CO·O or PhO, "single elimination" when R = MeS or Ph·CO·NH, and dissociation when R = Ph·CH$_2$·NH. The last two reactions are well known and it is unnecessary to discuss them further; so far as we know, however, the "double elimination" reaction is new and so warrants some discussion.

Before discussion of the reaction its potentialities as a new method for the protection of carboxyl and phenolic hydroxyl groups in sensitive compounds may be pointed out; for instance, such a compound could be converted into the 2-methylthioethyl ester or ether, the derivative subjected to other desired reactions, and the protecting group eventually removed by conversion into the methiodide followed by very mild alkaline treatment.

A thorough kinetic study of the double elimination reaction was not possible, so our discussion of the mechanism of the reaction is necessarily speculative. Our experimental data do not in themselves show whether the liberation of dimethyl sulphide precedes, follows, or is simultaneous with that of benzoic acid (or phenol). Let us consider the possible steps in a two-stage mechanism; it is at once clear that both stages must be eliminations since, were either of them a hydrolysis, the two-carbon reaction product would necessarily be, not acetylene, but acetaldehyde (vinyl alcohol), *e.g.*:

$$RO\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- \xrightarrow{\text{elimination}} HI + SMe_2 + RO\cdot CH{:}CH_2 \xrightarrow{\text{hydrolysis}} ROH + HO\cdot CH{:}CH_2$$

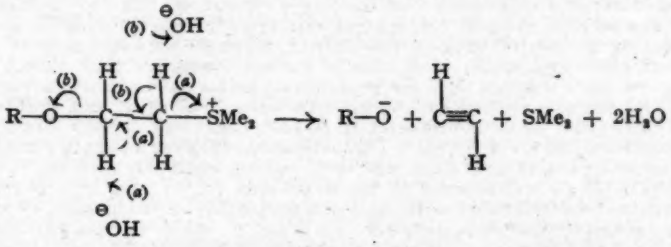
There remain, therefore, only two possible two-stage routes, *viz.*:

(A) $$RO\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- \longrightarrow \underset{\text{(XVI.)}}{HI + SMe_2 + RO\cdot CH{:}CH_2} \longrightarrow ROH + CH{:}CH$$

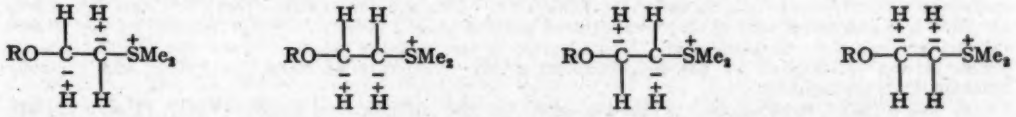
(B) $$RO\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- \longrightarrow ROH + \underset{\text{(XVII.)}}{CH_2{:}CH\cdot \overset{+}{S}Me_2\}I^-} \longrightarrow CH{:}CH + HI + SMe_2$$

Neither vinyl benzoate (XVI; R = Ph·CO) nor phenyl vinyl ether (XVI; R = Ph) appears to be specially sensitive to alkali, and so Route (A) may be discarded. The perchlorate of (XVII) was prepared by Hofmann, Höbold, and Quoos (*Annalen*, 1912, **386**, 317) who make no mention of any marked instability to alkali; neurine iodide, the nitrogen analogue of (XVII), is alkali-stable (cf. Renshaw and Ware, *J. Amer. Chem. Soc.*, 1925, **47**, 2993), and the corresponding hydroxide decomposes on distillation into trimethylamine, dimethylvinylamine, and acetaldehyde (Meyer and Hopff, *Ber.*, 1921, **54**, 2278); clearly Route (B) is, by itself, no more acceptable than Route (A).

We are thus led to postulate some kind of single-stage process, such as :



in which the two electronic processes (*a*) and (*b*) (which correspond to Routes A and B respectively) are coupled in some way, perhaps somewhat along the lines suggested by Robinson (*J.*, 1941, 220) for the benzidine change. The same idea may be expressed in different terms (cf. Hughes and Ingold, *ibid.*, p. 608) as a lowering of the activation energy resulting from resonance between the various possible ionic structures of the activated molecule :



In either case the necessary conditions for the occurrence of " double elimination " are, first, the presence on the α-carbon atom of a positively charged atom with a sufficient tendency to lose its positive charge [providing the driving force of electronic process (*a*)] and, secondly, the presence on the β-carbon atom of a sufficiently powerfully electron-attracting group [providing the driving force of electronic process (*b*)]. The first of these requirements probably explains why similar phenomena are not, apparently, exhibited by the nitrogen analogue of (VI), *viz.*, benzoylcholine (cf. Easson and Stedman, *Proc. Roy. Soc.*, 1936, *B*, **121**, 142; cf. acetylcholine, Renshaw and Bacon, *J. Amer. Chem. Soc.*, 1926, **48**, 1726; Kahane and Rousseau, *Bull. Soc. chim.*, 1939, **6**, 647). The second requirement fits in well with our observation that, of the five compounds of type (IV) which we have investigated, only those in which RH is most acidic [*viz.*, (VI) in which RH = Ph·CO_2H and (VIII) in which RH = PhOH] show the " double elimination " reaction.

Experimental.

1. *Dimethyl-2-benzoyloxyethylsulphonium Iodide.*—(a) *Preparation.* Methyl 2-hydroxyethyl sulphide (51 g.) was added slowly, with cooling and shaking, to a mixture of benzoyl chloride (86 g.) and dry pyridine (60 g.). After being heated on the water-bath for 2 hours, the mixture was cooled and treated with water. The precipitated oil was taken up in light petroleum (b. p. 40—60°), dried, and distilled, yielding 54 g. (50%) of *methyl 2-benzoyloxyethyl sulphide* (V) as a colourless oil, b. p. 137—138°/2·5 mm. (Found : C, 61·2; H, 5·9. $C_{10}H_{12}O_2S$ requires C, 61·2; H, 5·1%). This sulphide (14 g.) was kept at room temperature for 20 hours with methyl iodide (12 g.). The resulting crystalline mass was washed with dry ether and twice recrystallised from absolute alcohol, yielding *dimethyl-2-benzoyloxyethylsulphonium iodide* (VI) as colourless plates, m. p. 128—129° (decomp.) (Found : C, 39·0; H, 4·4. $C_{11}H_{15}O_2IS$ requires C, 39·1; H, 4·5%). The *picrate* crystallised from acetone in silky yellow needles, m. p. 151—152° (Found : C, 46·4; H, 3·8. $C_{17}H_{17}O_9N_3S$ requires C, 46·4; H, 3·9%).

(b) *Isolation of alkali fission products.* The sulphonium iodide (VI) (11·6 g.) was slowly distilled with 10% sodium hydroxide solution (33 c.c.) for 2 hours. The volatile oil which collected (1·3 g.) was identified as dimethyl sulphide (62% yield) by its b. p. (37—38°) and by conversion into the mercurichloride, m. p. and mixed m. p. 149—151°; the presence of a little methyl iodide was shown by the deposition of a small amount of trimethylsulphonium iodide, decomp. 215°, when the volatile oil was kept for a few days. Exhaustive ether extraction of the aqueous residue in the reaction flask failed to yield any methyl 2-hydroxyethyl sulphide; acidification of the aqueous residue yielded benzoic acid (4·2 g.; 100%), m. p. and mixed m. p. 121—122°. In a separate experiment, the presence of acetylene

in the gaseous products of the decomposition was demonstrated by the formation of a red precipitate of copper acetylide with cuprous chloride–hydroxylamine.

(c) *Quantitative experiments.* The rate of production of acid in dilute aqueous solution at 25° at pH 10 (phenolphthalein) and pH 11 (alizarin-yellow) was determined by continuous titration with baryta, using the apparatus of Powell and Trendall (*Chem. and Ind.*, 1943, **62**, 368). The velocity constants given on p. 767 were obtained by the usual logarithmic plotting method, the experimental points (20—40 for each experiment) falling satisfactorily on straight lines over the major portion of the experiment. The rate of hydrolysis at pH 7·4 and 37° was determined manometrically in a Warburg apparatus using bicarbonate buffer.

For comparative purposes, since the sulphide (V) is very sparingly soluble in water, its rate of fission was compared with that of the sulphonium iodide (VI) by continuous titration at 25° in 60% alcohol, alizarin-yellow being used as indicator, with the results quoted on p. 767.

2. *Dimethyl-2-phenoxyethylsulphonium Iodide.*—(a) *Preparation.* Methyl 2-chloroethyl sulphide (55 g.) was added to a solution of phenol (47 g.) and sodium hydroxide (20 g.) in 95% alcohol (500 c.c.). After 4 hours' refluxing the neutral product was filtered, concentrated under reduced pressure, diluted with water, and extracted with ether. The ethereal extract contained much phenol and was washed with 10% sodium hydroxide solution until the washings no longer gave a positive reaction with Folin's phenol reagent. The extract, washed once more with water, was dried and distilled, giving *methyl 2-phenoxyethyl sulphide* (VII) as a colourless oil, b. p. 120°/7 mm., $n_D^{18°}$ 1·5419 (Found: C, 64·05; H, 6·95. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%). This substance still gave a negative reaction with Folin's phenol reagent after being boiled for 5 mins. with 40% sodium hydroxide solution.

The sulphide (VII) (30 g.) was refluxed on the water-bath for an hour with methyl iodide (51 g.). The almost solid product was triturated with ether and separated; crystallisation from methanol–ether yielded *dimethyl-2-phenoxyethylsulphonium iodide* (VIII) (34 g.; 61%) in beautiful leaflets, m. p. 104° (decomp.) (Found: C, 38·9; H, 5·0. $C_{10}H_{15}OIS$ requires C, 38·7; H, 4·85%).

(b) *Isolation of alkali fission products.* The sulphonium iodide (VIII) (15·5 g.; 0·05 mol.) was distilled with 2N-sodium hydroxide (100 c.c.), distillation being stopped when no more oil came over (15 mins.). The oil was separated, dried, and distilled. The low-boiling fraction (1·2 g.; 39%) was identified as dimethyl sulphide by b. p. (37—42°) and by conversion into the mercurichloride, m. p. and mixed m. p. 148°; the presence of a little methyl iodide was shown by the deposition of a small amount of trimethylsulphonium iodide, decomp. 215°, on keeping. The high-boiling fraction (1·4 g.; 9%), b. p. 108—110°/4 mm., was identified as methyl 2-phenoxyethyl sulphide (VII) by conversion into the methiodide (VIII), m. p. and mixed m. p. 102—103°. The aqueous residue from the alkali fission was acidified and extracted with ether; evaporation yielded phenol (4·0 g.; 85%), identified by conversion into tribromophenol and picric acid. In a separate experiment the presence of acetylene in the gaseous products was established by the formation of a red precipitate of copper acetylide with cuprous chloride–hydroxylamine.

(c) *Quantitative experiments.* M/100-Solutions of the sulphonium iodide (VIII) in appropriate buffers (M/10-borate for pH 8, 9, 10, and 11; M/15-phosphate for pH 7·4) were kept at specified temperatures for various times. To 1 c.c. of the resulting solutions 5 drops of Folin's phenol reagent were added, followed by 1 c.c. of 10% sodium hydroxide. After 5 mins.' keeping the mixture was centrifuged and the supernatant liquid matched visually, after suitable dilution, with standards prepared from M/1000-phenol. The results, expressed as % fission, were as follows:

pH.	Temp.: 25°.	37°.	100°.
7·4	—	2% in 48 hrs.	10% in 1 min.
8·0	—	2% in 16 hrs.	10% in 1 min.
9·0	—	10% in 16 hrs.	20% in 1 min.
10·0	5% in 3½ hrs.	15% in 16 hrs.	100% in 1 min.
11·0	10% in 1 hr.	33% in 16 hrs.	100% in 1 min.
12·0	100% in 20 mins.	—	100% in 1 min.

3. *Dimethyl-2-methylthioethylsulphonium Iodide* (IX).—(a) *Preparation.* 1 : 2-Bismethylthioethane (10 g.) was refluxed on the water-bath for 2½ hrs. with methyl iodide (12 g.) and alcohol (5 c.c.). After cooling, the yellow crystalline product was washed with acetone and recrystallised from alcohol, from which the *iodide* (IX) (14·2 g.; 64%) separated in prisms, m. p. 94—95° (Found: C, 22·9; H, 4·8; I, 48·4. $C_5H_{13}IS_2$ requires C, 22·7; H, 4·9; I, 48·1%).

(b) *Isolation of alkali fission products.* The sulphonium iodide (IX) (22 g.) was slowly distilled with 10% sodium hydroxide solution (134 c.c.) for 2½ hours, the distillate being collected in two portions. The first portion contained 8·1 g. of a light oil which was separated, dried, and heated on the water-bath for 30 mins. with thiophenol (2·5 g.); fractionation of the product yielded dimethyl sulphide, b. p. 37—38° (mercurichloride, m. p. and mixed m. p. 151—152°), which contained a little methyl iodide since it deposited trimethylsulphonium iodide, decomp. 212°, on keeping, and phenyl 2-methylthioethyl sulphide, b. p. 117°/2 mm. (mercurichloride, m. p. and mixed m. p. 81—82°), derived from methyl vinyl sulphide present in the fission product. The oil in the second portion of the fission distillate was identified as 1 : 2-bismethylthioethane by conversion into the mercurichloride, m. p. and mixed m. p. 106—107°.

In a separate experiment no acetylene could be detected in the gaseous products of the fission; a positive nitroprusside reaction was given by the reaction mixture after 2—3 mins.' boiling but disappeared later.

(c) *Quantitative experiments.* Iodometric titration of M/100-solutions of the sulphonium iodide (IX) in M/10-borate buffers, pH 10, 11, and 12, kept at 25° for periods up to 5½ hrs., revealed no appreciable thiol formation.

4. *Dimethyl-2-benzamidoethylsulphonium Iodide.*—(a) *Preparation.* Methyl 2-aminoethyl sulphide was best prepared by the following application of the method of Brighton and Reid (*J. Amer. Chem. Soc.*,

1943, **65**, 458): An alcoholic solution of sodium thiomethoxide (from 9·3 g. of sodium, 63 g. of methyl*iso*thiourea sulphate, and 150 c.c. of absolute alcohol) was added to an alcoholic solution of 2-bromoethylamine (from 82·5 g. of the hydrobromide, 9·3 g. of sodium, and 150 c.c. of absolute alcohol), and the mixture heated under reflux for 4 hrs.; sodium bromide was filtered off from the cooled solution, and the alcohol distilled off after addition of concentrated hydrochloric acid (31 c.c.). The residue was treated with 50% potassium hydroxide solution, and the liberated base extracted with ether, dried, and distilled, b. p. 148—150° (25·5 g., 50%).

Methyl 2-aminoethyl sulphide (30 g.) was added, in small portions, with cooling and shaking, to a mixture of benzoyl chloride (50 g.) and pyridine (100 c.c.). After being heated on the water-bath for an hour, the product was cooled and diluted with water; crystallisation of the precipitated solid from benzene–light petroleum (b. p. 60—80°) yielded methyl 2-benzamidoethyl sulphide (28 g.; 47%) in pearly plates, m. p. 60—61° (Schneider, *Annalen*, 1912, **386**, 338, gives m. p. 57°) (Found: C, 61·1; H, 6·8; N, 7·8. Calc. for $C_{10}H_{13}ONS$: C, 61·5; H, 6·7; N, 7·2%). This sulphide (16 g.) was kept for 24 hrs. at room temperature with methyl iodide (22 g.) in absolute alcohol (15 c.c.); crystallisation of the precipitate from alcohol yielded *dimethyl-2-benzamidoethylsulphonium iodide* (X) (21·7 g.; 80%) in plates, m. p. 121—122° (Found: C, 39·4; H, 4·7; N, 4·6. $C_{11}H_{16}ONIS$ requires C, 39·2; H, 4·75; N, 4·2%).

(b) *Isolation of alkali fission products.* The sulphonium iodide (X) (16 g.) was slowly distilled (2 hrs.) with 10% sodium hydroxide solution (76 c.c.). A light oil distilled over first, followed by a heavy oil which only distilled over with difficulty. The reaction mixture was finally refluxed for a further hour.

The light oil was identified as dimethyl sulphide (65% yield) by conversion into the mercurichloride, m. p. and mixed m. p. 150—151°. The heavy oil remaining in the flask was extracted with ether, dried, and distilled; the distillate, b. p. 80—81°/1 mm., was identified as 2-phenyl-4 : 5-dihydrooxazole (XII) (3 g.; 43%) (Found: C, 73·6; H, 6·5; N, 9·3. Calc. for C_9H_9ON: C, 73·5; H, 6·1; N, 9·5%) by conversion into the hydrochloride, plates, m. p. 81° (lit. m. p. 81°), from light petroleum (b. p. 40—60°), and the picrate, yellow needles from benzene, m. p. and mixed m. p. 177—178°, which, on boiling with water, yielded 2-benzoyloxyethylamine picrate, orange plates from water, m. p. and mixed m. p. 195°. The aqueous residue in the reaction flask was acidified, yielding 0·6 g. (11%) of benzoic acid, m. p. and mixed m. p. 119—120°. No acetylene could be detected as a reaction product.

In a control experiment, the compound (XII) (Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079) was boiled with 10% sodium hydroxide solution for 3 hrs.; 65% of the oxazoline was recovered unchanged and a 20% yield of benzoic acid was isolated. In a second control experiment, methyl 2-benzamidoethyl sulphide was refluxed for 1·25 hrs. with 10% sodium hydroxide solution; 86% was recovered unchanged, some 2·5% being hydrolysed to benzoic acid and methyl 2-aminoethyl sulphide (picrate, m. p. and mixed m. p. 119—120°).

5. *Dimethyl-2-benzylaminoethylsulphonium Iodide.*—(a) *Preparation.* Following Dawson (*J. Amer. Chem. Soc.*, 1933, **55**, 2070), methyl 2-chloroethyl sulphide (22·1 g.) and benzylamine (21·4 g.) were refluxed on the water-bath for 23 hrs. with absolute alcohol (100 c.c.) and anhydrous sodium carbonate (21·2 g.). The cooled product was filtered and evaporated to small bulk under reduced pressure; the residue was treated with 30% potassium hydroxide solution, extracted with ether, and dried over potassium hydroxide. Two distillations yielded 8 g. (25%) of *methyl 2-benzylaminoethyl sulphide* (XIV), b. p. 139—140°/5·5 mm. (Found: C, 66·8; H, 8·2; N, 7·4. $C_{10}H_{15}NS$ requires C, 66·2; H, 8·3; N, 7·7%), which was characterised as its *hydrochloride*, plates, m. p. 238—240°, from alcohol (Found: C, 54·8; H, 7·7. $C_{10}H_{16}NSCl$ requires C, 55·2; H, 7·4%), and its *picrate*, fine needles from aqueous alcohol, m. p. 116—117° (Found: C, 46·7; H, 4·2. $C_{16}H_{18}O_7N_4S$ requires C, 46·8; H, 4·4%). This sulphide (XIV) (11·1 g.), in absolute alcohol (20 c.c.), was kept for some days with methyl iodide (8·7 g.); the crystalline precipitate obtained on adding ether was recrystallised from alcohol–ether, yielding *dimethyl-2-benzylaminoethylsulphonium iodide* (XIII) (5·5 g.; 30%) as shining plates, m. p. 132—133° (Found: C, 40·7; H, 5·8; N, 3·9. $C_{11}H_{18}NIS$ requires C, 40·9; H, 5·6; N, 4·3%).

(b) *Alkaline fission.* (i) Isolation of reaction products. The sulphonium iodide (XIII) (8 g.) was slowly distilled for 2 hrs. with 10% sodium hydroxide, 25 c.c. of water being added during this period. The distillate, collected in two portions, contained 2 g. of an oil lighter than water and 0·8 g. of an oil heavier than water; the residue in the distilling flask contained an oil and deposited a crystalline solid on cooling.

The light oil in the distillate was separated, dried, and distilled, yielding three fractions. Fraction (1), 0·2 g., b. p. 25—60°, was too small for further separation but was probably a mixture of dimethyl and methyl vinyl sulphides; fraction (2), 0·65 g., b. p. 60—155°, was basic and was identified as benzyldimethylamine by conversion into the picrate, yellow needles from water, m. p. and mixed m. p. 94—95°. Fraction (3), 0·4 g., b. p. >155°, was identified as methyl 2-benzylaminoethyl sulphide (XIV) by conversion into the picrate, m. p. 114—115°, mixed m. p. 116—117°. The heavy oil in the distillate and that remaining in the reaction flask were collected by ether extraction and identified as methyl 2-benzylaminoethylsulphide (XIV) by conversion into the picrate, m. p. and mixed m. p. 115—116°, and hydrochloride, m. p. and mixed m. p. 235—237°. The crystalline solid remaining in the reaction flask was not extracted by ether; it was filtered off and recrystallised from alcohol, forming long needles, m. p. 149—150°, identified as benzyldimethyl-(2-methylthioethyl)ammonium iodide (XV) by mixed m. p., 150—151°, with a synthetic specimen (below). Acetylene could not be detected as a reaction product.

In a control experiment the sulphide (XIV) was recovered unchanged (96% yield) after refluxing for 2½ hrs. with 10% sodium hydroxide solution.

(ii) Quantitative experiments. No liberation of free primary amino-groups could be detected, a volumetric Van Slyke apparatus being used, in 2 hrs. when the sulphonium iodide (XIII) was kept in M/100-solution in water at 25°, in borate buffer pH 12 at 25° and 100°, or in 10% sodium hydroxide at 25°.

(iii) Synthesis of reaction products. Methyl 2-benzylaminoethyl sulphide (XIV) (3 g.) was treated, with shaking, with methyl iodide (5 g.) and 10% sodium hydroxide solution (10 c.c.). On cooling *benzyldimethyl-(2-methylthioethyl)ammonium iodide* (XV) crystallised out, and recrystallised from alcohol

in long silky needles, m. p. 150—151° (Found: C, 42·6; H, 5·9; I, 36·9. $C_{12}H_{20}NIS$ requires C, 42·7; H, 5·9; I, 37·7%). This iodide (XV) (13·8 g.) was distilled for 3 hrs. with 10% sodium hydroxide solution (56 c.c.); on cooling, 3·3 g.(24%) of unchanged iodide crystallised out in the distillation flask. The volatile product (5·7 g.) was separated, dried, and distilled, yielding two fractions. Fraction (1), b. p. 65—70°, was identified as methyl vinyl sulphide by heating on the water-bath with thiophenol, whereupon it yielded phenyl 2-methylthioethyl sulphide, characterised as its *mercurichloride*, m. p. and mixed m. p. 81—82° (Found: C, 24·0; H, 3·0. $C_9H_{13}Cl_2S_2Hg$ requires C, 23·7; H, 2·6%). Fraction (2), b. p. 165—172°, was identified as benzyldimethylamine by conversion into the picrate, m. p. and mixed m. p. 94—95°.

We are indebted to the Director General of Scentific Research (Defence), Ministry of Supply, for permission to publish this work, and to Mr. J. E. Cave-Browne-Cave for technical assistance. Micro-analyses were carried out by Mr. G. Ingram.

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[*Received, September 20th*, 1946.]

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149. α-cyclo*Hexyl*-β-*propylacrylic Acid from* cyclo*Hexanol*.

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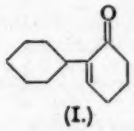
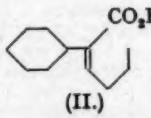
The acid formed from *cyclo*hexanol at 300° in presence of sodium *cyclo*hexyloxide has been shown to be 1-*cyclo*hexylpent-1-ene-1-carboxylic (α-*cyclo*hexyl-β-propylacrylic) acid. The mechanism of its formation is discussed.

Guerbet (*Compt. rend.*, 1912, **155**, 1156) observed that if a solution of sodium *cyclo*hexyloxide in excess of *cyclo*hexanol was heated at about 300°, an acid was formed to which he ascribed the formula $C_{11}H_{21}\cdot CO_2H$. This acid, which was obtained in our experiments in an average yield of 0·21 mol. per mol. of sodium *cyclo*hexyloxide, was found to have the formula $C_{12}H_{20}O_2$ and to contain one double bond and, therefore, one ring. Its hydrogenation product has been identified as 1-cyclo*hexylpentane*-1-*carboxylic acid* (III). It is submitted that Guerbet's acid is the corresponding 1-cyclo*hexylpent*-1-*ene*-1-*carboxylic acid* (α-*cyclo*hexyl-β-propylacrylic acid) (II) and that it originates from the hydrolytic fission of 2-*cyclo*hexyl-2-*cyclo*hexenone (I). This is in accord with the view put forward by Weizmann, Bergmann, and Haskelberg (*Chem. and Ind.*, 1937, **56**, 587) that the Guerbet condensations of alcohols proceed *via* the corresponding carbonyl compounds and the self-condensation (crotonisation) products of the latter. The so-called "*cyclo*hexylidene-*cyclo*hexanone" which would be expected to be formed from *cyclo*hexanol on the basis of this mechanism is, according to Wallach (*Annalen*, 1911, **381**, 96), in equilibrium with (I).

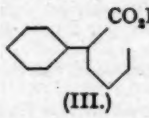
The synthesis of (III) was carried out by butylation of ethyl *cyclo*hexenylcyanoacetate, simultaneous hydrolysis and half-decarboxylation of the product so obtained, and finally catalytic hydrogenation. An attempt to butylate ethyl *cyclo*hexylmalonate was unsuccessful.



(I.)



(II.)



(III.)

Experimental.

1-cyclo*Hexylpent*-1-*ene*-1-*carboxylic Acid* (II).—The *acid* was obtained according to Guerbet (*loc. cit.*); b. p. 180°/14 mm.; 168°/6 mm.; $d_{20°}^{20°}$ 0·9822; $n_D^{20°}$ 1·4848 (Found: C, 74·0; H, 10·5; bromine number, 80·6; *M* (in camphor) 196, (by titration) 208; [*R*], 57·76. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%; bromine number, 80·0; *M*, 196; [*R*], 56·51). The molecular refraction is in accord with (II); a molecular exaltation of about 0·6 would be expected for such a highly-substituted conjugated system. An alcoholic solution of *p*-bromophenacyl bromide (2·8 g.) was added to an aqueous solution (10 c.c.) of the sodium salt of the acid (2 g.), and the mixture was boiled for 4 hours. The oil, which separated upon cooling, solidified spontaneously. From light petroleum, the p-*bromophenacyl* ester crystallised in shiny leaflets, m. p. 67°. Yield, almost quantitative (Found: C, 61·2; H, 6·4; Br, 21·0. $C_{20}H_{25}O_3Br$ requires C, 61·1; H, 6·4; Br, 20·4%).

Hydrogenation.—A solution of the Guerbet acid (14·5 g.) in propyl alcohol (100 c.c.) was hydrogenated with palladium–barium sulphate as catalyst at ordinary temperature. In 3 hours, the theoretical quantity of 1700 c.c. of hydrogen had been absorbed. Distillation gave the hydrogenated acid, b. p. 182·5—183°/14 mm., which was later identified as 1-cyclo*hexylpentane*-1-*carboxylic acid* (Found: C, 72·8; H, 11·0. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·1%). The p-*bromophenacyl* ester, prepared as above, solidified at 0° after addition of water, and crystallised in large, shiny leaflets from light petroleum; m. p. 45—46° (Found: C, 60·9; H, 6·3; Br, 20·6. $C_{20}H_{27}O_3Br$ requires C, 60·8; H, 6·8; Br, 20·3%).

Synthesis.—Ethyl *cyclo*hexenylcyanoacetate (Harding, Haworth, and Perkin, *J.*, 1908, **93**, 1958) (b. p. 165°/16 mm.) (58 g.) and butyl bromide (41·1 g.) were added to a solution of sodium (7 g.) in absolute propyl alcohol (150 c.c.). After 4 hours at the boiling point of the solution, reaction was complete. The sodium bromide was removed by filtration, the solvent under reduced pressure, and the residue was treated with water and ether. *Ethyl* cyclo*hexenylbutylcyanoacetate* boiled at 173°/16 mm. Yield, 42 g. (Found: C, 72·6; H, 9·6; N, 6·0. $C_{15}H_{23}O_2N$ requires C, 72·0; H, 9·2; N, 5·6%).

Hydrolysis of the ester presented unusual difficulties. Boiling alcoholic potassium hydroxide was practically without effect. The ester (21 g.) was heated with potassium hydroxide (40 g., 8 mols.) in water (50 c.c.), in an oil-bath at 180° for 24 hours. The cooled reaction product consisted of a solid precipitate and an oily top layer which dissolved on dilution with some water. Acidification liberated carbon dioxide, and extraction with ether then gave 1-cyclo*hexenylpentane*-1-*carboxylic acid*, b. p. 156°/7 mm., after a substantial head fraction which was not further investigated. Yield, 8 g. (Found: C, 73·0; H, 9·9. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%).

1-cyclo*Hexylpentane*-1-*carboxylic Acid* (III).—The unsaturated acid (4 g.) was hydrogenated in propyl alcohol (25 c.c.) with palladium–barium sulphate as catalyst at room temperature. The theoretical quantity of hydrogen was absorbed in 4 hours. The reduction product boiled at 159—160°/9 mm. (Found: C, 72·6; H, 11·1. Calc. for $C_{12}H_{22}O_2$: C, 72·7; H, 11·1%).

The *p*-bromophenacyl ester had m. p. 46—47° and proved identical with that prepared from the hydrogenation product of the Guerbet acid.

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150. *The Configuration of Naturally Occurring Mixed Glycerides. Part III. The Configuration of the Major Component Glycerides of Piqui-a Fruit-coat Fat.*

By M. L. MEARA.

Piqui-a fruit-coat fat has been separated by crystallisation into mono-oleo- and dioleo-glycerides. The mono-oleo-glycerides have been shown to consist of β-oleodipalmitin, no unsymmetrical isomer having been found. Low-temperature crystallisation of the dioleoglycerides followed by crystallisation of the hydrogenated derivatives has shown that both symmetrical and unsymmetrical palmitodioleins and palmito-oleolinoleins occur in this fat.

THE fruits of the piqui-a (*Caryocar villosum*) contain fatty matter in both the kernel and the mesocarp. The characteristics of these fats have been described by Georgi (*Malayan Agric. J.*, 1929, **17**, 166) and a fuller examination of the component acids and glycerides has been reported by Hilditch and Rigg (*J. Soc. Chem. Ind.*, 1935, **54**, 109T), who showed that the fats were quantitatively similar and unusually rich in palmitic acid, the component fatty acids of the fruit-coat fat being myristic, 1·8; palmitic, 47·3; stearic, 1·7; oleic, 47·3; linoleic, 1·9% (mol.). Oxidation of a portion of the fat with permanganate in acetone gave 2% of fully saturated glycerides, indicating that the fat conforms closely to the " evenly distributed " type of seed fats, differing from palm oil, which, at this palmitic acid content, would contain 7—10% of fully saturated glycerides. From this Hilditch and Rigg deduced that piqui-a fruit-coat fat consisted chiefly of oleodipalmitins and palmitodioleins together with small amounts of minor components.

Another portion of the fruit-coat fat was hydrogenated and the product systematically crystallised from benzene. Tristearin was shown to be absent, indicating the absence of triolein in the fat. Difficulty was encountered in the separation of pure palmitodistearin, and Hilditch and Rigg concluded that this was due not only to the presence of more stearodipalmitin than in fats such as hydrogenated cotton-seed oil (where this difficulty had not arisen), but also to the probable presence of both α- and β-palmitodistearins and stearodipalmitins. This view received considerable support from a similar examination of a partially hydrogenated specimen (iodine value, 7·0).

Because of this anomaly and of the fact that piqui-a fruit-coat fat must be one of the simplest mixtures of mixed triglycerides occurring in a natural fat, a portion of the specimen used in the earlier investigation of Hilditch and Rigg has been re-investigated in the manner recently described by Meara (Parts I and II of this series, *J.*, 1945, 22, 23).

EXPERIMENTAL.

Piqui-a fruit coat fat (saponification equiv. 281·6, iodine value 47·8) was neutralised by shaking an ethereal solution with 10% aqueous potassium carbonate solution, followed by washing and removal of the solvent. The fat (200 g.) was then exhaustively crystallised from acetone and from ether until a series of crystalline fractions was obtained which on further recrystallisation gave no further change in iodine value. In this way 5 fractions (A—E) of iodine value 30·2, 30·1, 29·9, 29·9, and 30·2, respectively, were

obtained. Each fraction was investigated separately in case, if both symmetrical and unsymmetrical oleodipalmitins occurred in this fat, their partial separation might have been effected during the exhaustive crystallisation. After a final slow recrystallisation from acetone, the transition and melting points of each fraction were determined (Table I) in the manner described in Part I (*loc. cit.*).

[The nomenclature used by Daubert *et al.* for the polymorphic forms has been adopted in the tables which follow (cf. Part I, 1945, 22). The forms IV, III, II, I correspond respectively to Malkin's vitreous, α, β′, and β.]

TABLE I.

Transition and melting points of oleodipalmitin.

Fraction.	Weight (g.).	IV.	III.	II.	I.
A	20·0	13·5—14°	17·5—18°	35°	36·8—37°
B	10·0	13—14	17—18	35	36·8—37
C	14·1	12·5—14	17—18	34—35	36·5—37
D	27·1	12·5—13·5	17—18	34—35	36·5—37
E	12·2	13—14	17—18	35	36·7—37
Synthetic β-oleodipalmitin *		12·0	20·8	30·4	35·2
,, α- ,, *		18·5	29·8	—	34·5

* Daubert *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 690; *Oil and Soap*, 1945, **22**, 113.

A portion of each fraction was hydrogenated at 100° in the presence of Raney nickel, hydrogen being readily and quantitatively absorbed at this temperature, which is low enough to inhibit any tendency to acyl migration (now known to occur to some small extent in the presence of nickel on kieselguhr at 180°; cf. Atherton and Hilditch, *J.*, 1941, 527). The stearodipalmitins obtained were crystallised from ether and their transition and melting points determined, the respective values (Table II) being identical within experimental error, and identical with the now well-authenticated values for β-stearodipalmitin.

TABLE II.

Transition and melting points of the stearodipalmitins.

	IV.	III.	II.	I.
A—E	48—49°	59—60°	65°	67·7—68°
Synthetic β-stearodipalmitin *	49	59	65	68
,, α- ,, †	46·5	55	59·5	62·5

* Malkin and Meara, *J.*, 1939, 103. † Carter and Malkin, *J.*, 1939, 577.

The liquid fractions, iodine values 62·1 and 58·0, which consisted mainly of palmitodiolein with some palmito-oleolinolein and traces of triolein, were crystallised separately from acetone at low temperatures to give 3 main fractions, F, G, and H (weights 36·5, 17·7, and 16·7 g.; iodine values 59·5, 59·7, and 70·0 respectively). These were hydrogenated and exhaustively crystallised from ether.

From H a small quantity of material, m. p. 70—72°, was obtained, indicating the presence of a trace of tristearin, m. p. 71°, but this was not further investigated The bulk of the remaining material had m. p. 64—65° unchanged by further recrystallisation. Transition and melting points of this fraction were then determined and are recorded in Table III.

Crystallisation of G gave a small yield of material, m. p. 67—67·2°, consisting mainly of β-palmitodistearin together with a fraction, m. p. 64·5—66·5° not significantly changed by further recrystallisation. Satisfactory transition points could not be obtained for this fraction.

Crystallisation of F gave a main fraction, m. p. 67—68°, and a small yield of material, m. p. 63—64°. More detailed thermal data for these fractions are given in Table III.

TABLE III.

Transition and melting points of palmitodistearins.

Fraction.	IV.	III.	II.	I.
F (mainly)	49—50°	55—56°	63—64°	67—68°
F (small quantity)	48	55—56	59—60	63—64
G ,, ,,	50	55	62·5—63·5	67—67·2
G (mainly)	44—48	52—55	—	64·5—66·5
H (mainly)	48	56	60	64·5—65
Synthetic β-palmitodistearin *	50	56	64	68
,, α- ,, *	50	57	61	65

* Malkin and co-workers (*locc. cit.*).

DISCUSSION.

It is evident from Tables I and II that the oleodipalmitin occurring in piqui-a fruit-coat fat consists wholly of the symmetrical isomer. While the observed values in Table I are identical within experimental error they are not in complete accord with those obtained by Daubert *et al.* but resemble much more those of the β- than those of the α- (unsymmetrical) isomer.

The data for the derived stearodipalmitins (Table II) agree remarkably well with those for synthetic β-stearodipalmitin.

Thermal data for products of hydrogenation of the palmitodioleins present in piqui-a fruit-coat fat could only be determined after a much more rigorous crystallisation of the hydrogenated material. Table III, summarising the data obtained, indicates that fraction F consisted mainly of symmetrical palmitodistearin together with a small quantity of the unsymmetrical isomer. From fraction G a small quantity of pure symmetrical palmitodistearin was obtained, but the bulk of this fraction appeared to be a difficultly resolvable mixture of the two isomers. Fraction H, however, appeared to consist almost entirely of the unsymmetrical isomer.

Thus both α- and β-palmitodistearins occurred in the hydrogenated material from these fractions, a moderate separation of the parent dioleins having been obtained in the low temperature crystallisation of the more soluble portions of the original fat. Although the conditions of crystallisation and hydrogenation precluded any strictly quantitative estimate of the proportions of the various glycerides isolated, it is considered that the amounts of the unsymmetrical and symmetrical palmitodioleins in fractions F, G, and H were probably of the same order.

This investigation has therefore partially confirmed the earlier work of Hilditch and Rigg (*loc. cit.*) who, not having first separated mono-oleo- from dioleo-glycerides, were led by their results to postulate the probable occurrence of both α- and β-mono-oleodipalmitins and palmitodioleins. It is also seen that, if they can be isolated in a sufficiently high degree of purity, thermal examination either of the individual glycerides or of their hydrogenated products is sufficient to determine their structure, without the necessity of resorting to *X*-ray crystal analysis, as has been suggested by Daubert *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 167).

The author wishes to thank Professor T. P. Hilditch for his advice and criticism during this investigation.

THE UNIVERSITY, LIVERPOOL. [*Received, October 2nd*, 1946.]

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151. *Synthetic Antimalarials. Part XIV. Some 2-Arylamino-4-aminoalkylaminoquinazolines.*

By F. H. S. CURD, J. K. LANDQUIST, and F. L. ROSE.

The preparation of a series of 2-arylamino-4-aminoalkylaminoquinazolines is described. Many of the compounds show marked antimalarial activity against the endo-erythrocytic forms of *P. gallinaceum* in chicks but no activity against the exo-erythrocytic forms. In this respect they resemble the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines (Part I, *J.*, 1946, 343) and the corresponding 5 : 6-disubstituted pyrimidine derivatives described in Part VII (*J.*, 1946, 378) to which they are related structurally.

The preparative methods employed comprise (*a*) the reaction of an aminoalkylamine with a 2-arylaminoquinazoline bearing a labile group (Cl, OEt, OPh, SMe) in the 4-position, and (*b*) the stepwise reaction of 2 : 4-dichloroquinazoline with an aminoalkylamine and an arylamine.

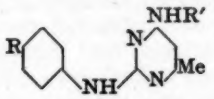
THE discovery of a new type of antimalarial structure in the 2-arylamino-4-dialkylamino-alkylamino-6-methylpyrimidines (I) described by Curd and Rose in Part I (*loc. cit.*) provided a novel lead for chemotherapeutic investigations and it has been followed up in numerous directions with varied degrees of success.

At the inception of this work it appeared as if antimalarial activity was associated with the attachment to a heterocyclic nucleus of an aminoalkyl group and an aryl group through linkages capable of forming prototropic systems with the central nucleus, as in (I). The replacement of the pyrimidine nucleus in (I) by other nitrogen-containing heterocyclic systems was an obvious development, and some analogous quinazoline derivatives of type (II) are now described. In addition to its relationship to (I), type (II) was clearly even more closely related to the active 2-arylamino-4-aminoalkylamino-5 : 6-disubstituted pyrimidines such as for instance (III) described in Part VII (*loc. cit.*).

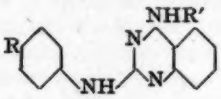
Previously, quinazoline derivatives have not been investigated to any great extent as antimalarials. In view of the interest in the quinoline nucleus this is rather surprising and may be connected with the statement of Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797) that 4-dialkylaminoalkylaminoquinazolines including those carrying an additional substituent such as chloro-, nitro-, or amino- in the 6-position are devoid of antimalarial activity.

However, the results given in Table I show that the earliest compounds of the type now described possessed considerable antimalarial activity and this activity persisted over a wide range of chemical variants subsequently investigated.

It is proposed to hold over discussion of the bearing of these results on the hypotheses we have advanced relating chemical structure with antiplasmodial activity in our various related types of compounds until several complementary investigations have been completed. It may be pointed out, however, that quinazolines of type (II) would be expected to show qualitatively similar resonance and tautomeric phenomena to the related pyrimidines of type (I) except in so far as these become modified by the presence of the extra fused benzene nucleus. Our subsequent investigations in this field have therefore been designed, *inter alia*, to throw light on this point.



(I.)



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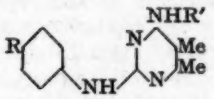

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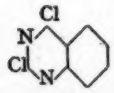
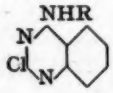
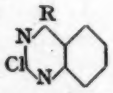


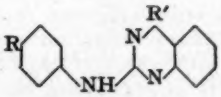
(IV.)



(V.)



(VI.)



(VII.)

The synthesis of compounds of type (II) was first essayed from 2 : 4-dichloroquinazoline (IV). The stepwise replacement of the two chlorine atoms in this compound with different amines, usually dyes or dye intermediates, has been described in E.P. 309,102 and in other patents, but while it was indicated that reaction probably occurred first at the 4-position no proof of this was given.

2 : 4-Dichloroquinazoline was found to react vigorously with two molecular proportions of γ-diethylaminopropylamine in the absence of a solvent to give 2 : 4-*bis*-(γ-*diethylaminopropylamino*)*quinazoline*, but with a cold dilute aqueous solution of the amine, using sodium hydroxide as acid-binding agent, only one chlorine atom was replaced and a compound formed that was later proved to be 2-*chloro*-4-γ-*diethylaminopropylaminoquinazoline* (V; R = $[CH_2]_3$·NEt_2). The latter reaction was then applied successfully to a number of other dialkylaminoalkylamines and substituted alkylamines such as ethanolamine. The yields were practically quantitative on the 2 : 4-dichloroquinazoline used and there was no evidence of the formation of any of the isomeric 4-chloro-2-substituted alkylaminoquinazolines. The compounds were found to be unexpectedly stable to hydrolysis by acid or alkali and could be distilled at pressures of 0·1 mm. or less.

Compounds of type (V) reacted smoothly with arylamines when heated together at 150°, or in a solvent such as acetic acid, or in boiling dilute hydrochloric acid (cf. Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127, 1131) to give 2-arylamino-4-aminoalkylaminoquinazolines. Thus (V; R = $[CH_2]_3$·NEt_2) and *p*-anisidine gave 2-p-*anisidino*-4-γ-*diethylaminopropylaminoquinazoline* (II; R = OMe; R' = $[CH_2]_3$·NEt_2) while (V; R = $[CH_2]_3$·NEt_2) with *p*-chloroaniline gave 2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (II; R = Cl, R' = $[CH_2]_2$·NEt_2).

The same compounds were also obtained in the following way. 2 : 4-Dichloroquinazoline was converted into 2-chloro-4-hydroxyquinazoline (VI; R = OH) (Lange and Sheibley, *J. Amer. Chem. Soc.*, 1931, **53**, 3867; 1933, **55**, 1188) by treatment with excess of 2N-sodium hydroxide (cf. E.P. 287,179). This on reaction with *p*-anisidine gave 2-p-*anisidino*-4-*hydroxyquinazoline* (VII; R = OMe, R' = OH), and with *p*-chloroaniline 2-p-*chloroanilino*-4-*hydroxyquinazoline* (VII; R = Cl, R' = OH), converted by the action of phosphoryl chloride into 4-chloro-2-*p*-anisidinoquinazoline (VII; R = OMe, R' = Cl) and 4-*chloro*-2-p-*chloroanilinoquinazoline* (VII; R = R' = Cl) respectively. (These two compounds were very labile and characterisation of the former was not possible.) Finally (VII; R = OMe, R' = Cl) was heated with γ-diethylaminopropylamine and (VII; R = R' = Cl) with β-diethylaminoethylamine. The identity of the final products made by the two methods lent support to the correctness of the assigned structures since there seemed little doubt that 2-chloro-4-hydroxyquinazoline had been correctly oriented. Thus, for instance, Lange and Sheibley (*J. Amer. Chem. Soc.*, 1932, **54**, 1994) brought this compound into reaction with aniline to give 2-anilino-4-hydroxyquinazoline (VII; R = H, R' = OH) identical with the product obtained

by condensing anthranilic acid with *N*-phenyl-*S*-methyl*iso*thiourea (cf. Wheeler, Johnson, and McFarland, *ibid.*, 1903, **25**, 797).

Further confirmatory proof of the structure of compounds of type (II), and therefore of their precursors of type (V; R = dialkylaminoalkyl), was provided by the following very convenient synthesis. It was known (Lange, Roush, and Asbeck, *J. Amer. Chem. Soc.*, 1930, **52**, 3696) that 2 : 4-dichloroquinazoline reacted with sodium phenoxide in ethanol to give 2-chloro-4-ethoxyquinazoline (VI; R = OEt) because reduction of this compound with zinc dust and acetic acid gave 4-ethoxyquinazoline identical with that made by the method of Bogert and May (*ibid.*, 1909, **31**, 510) from 4-chloroquinazoline and sodium ethoxide. *p*-Chloroaniline was therefore condensed with the 2-chloro-4-ethoxyquinazoline to give 2-p-*chloroanilino*-4-*ethoxyquinazoline* (VII; R = Cl, R′ = OEt) which was then brought into reaction with β-diethylaminoethylamine at 140—150°, with elimination of alcohol, to give (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) identical with the compound made by the previous methods.

Similarly 2-chloro-4-phenoxyquinazoline (VI; R = OPh) (Lange, Roush, and Asbeck, *loc. cit.*) and 2-*chloro*-4-*methylthioquinazoline* (VI; R = SMe) (prepared by treating 2 : 4-dichloroquinazoline with one equivalent of sodium thiomethoxide in cold alcohol) reacted with *p*-chloroaniline to give respectively 2-p-*chloroanilino*-4-*phenoxyquinazoline* (VII; R = Cl, R′ = OPh) and 2-p-*chloroanilino*-4-*methylthioquinazoline* (VII; R = Cl, R′ = SMe) both of which reacted with β-diethylaminoethylamine to give (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).

The greater lability of the 4-chlorine atom in 2 : 4-dichloroquinazoline noted by previous workers and confirmed in the present investigation differentiates this substance from 2 : 4-dichloropyrimidine and its homologues (2 : 4-dichloro-6-methyl- and 2 : 4-dichloro-5 : 6-dimethylpyrimidine) which yield a mixture of the two isomeric mono-condensation products on reaction with ammonia and amines. It resembles rather 2 : 4-dichloro-5-nitro- and 2 : 4-dichloro-5-nitro-6-methyl-pyrimidine in which mono-condensation occurs exclusively at the 4-position (cf. Isay, *Ber.*, 1906, **39**, 252; Gabriel and Colman, *ibid.*, 1901, **34**, 1234). Presumably the inductive effect of the aromatic nucleus in (IV), like a nitro-group in the pyrimidines mentioned above, renders the 4-position more accessible to attack by anionoid reagents.

The foregoing methods were used for the preparation of a variety of other quinazoline derivatives of type (II) in which the effect of variations in the aryl group and in the basic side chain was examined. In general these compounds formed colourless, crystalline, non-hygroscopic hydrochlorides which were used for biological tests.

The results of tests against the blood invasive forms of *P. gallinaceum* in chicks carried out by the method of Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139) are given in Table I, the method of expressing antimalarial activity being the same as in Part I (*loc. cit.*). The detailed biological results will be published elsewhere.

Experimental.

2 : 4-*Dichloroquinazoline* (IV).—The following method based on the work of Baddiley and Topham (*J.*, 1944, 678) was preferred to the earlier methods in the literature (cf. Gabriel and Colman, *Ber.*, 1905, **38**, 3559). 2 : 4-Dihydroxyquinazoline (20 g.), phosphoryl chloride (60 c.c.), and dimethylaniline (9 c.c.) were refluxed for 5½ hours. The mixture was then cooled slightly and poured on crushed ice (700 g.). The precipitated dichloroquinazoline was filtered off, washed acid free with ice–water, and dried (yield, 18·6 g.); m. p. 116—117°. It was best purified further by vacuum distillation.

2 : 4-*Bis*-(*γ-diethylaminopropylamino*)*quinazoline*.—2 : 4-Dichloroquinazoline (4 g.) was added to γ-diethylaminopropylamine (5·5 g.). When the ensuing violent reaction had subsided the mixture was heated for 2 hours at 130°. The cooled reaction mixture was extracted with 5% acetic acid (50 c.c.), the solution made strongly alkaline, and the liberated base taken into ether. Evaporation of the dried (K_2CO_3) ether solution and distillation of the residue gave the *quinazoline* as a viscous pale yellow oil, b. p. 206—208°/0·02 mm. (Found: N, 21·7. $C_{22}H_{38}N_6$ requires N, 21·8%). It formed a *tripicrate* which crystallised from 2-ethoxyethanol as yellow laminæ, m. p. 180° (Found: C, 44·8; H, 4·5; N, 19·3. $C_{22}H_{38}N_6,3C_6H_3O_7N_3$ requires C, 44·7; H, 4·4; N, 19·55%).

2-*Chloro*-4-*aminoalkylaminoquinazolines* (V).—Finely ground 2 : 4-dichloroquinazoline (20 g., 0·1 g.-mol.), water (200 c.c.), and the appropriate aminoalkylamine (0·1 g.-mol.) were stirred at room temperature. After 1 hour the mixture was made just alkaline to Clayton-yellow by the addition of 10N-sodium hydroxide solution, and further additions were then made at intervals to maintain the alkalinity until approximately 0·1 g.-mol. had been added (4—12 hours). The solution was then acidified (to Congo-red) with hydrochloric acid and filtered from unreacted 2 : 4-dichloroquinazoline. Addition of excess of sodium hydroxide solution then precipitated the *quinazoline* (sometimes as a hydrate) as an oil or gum which crystallised on standing or, after decantation of the aqueous layer, on trituration with ether. The product was collected, washed well with water, and dried at room temperature. It was normally used without further purification but if necessary this was best effected by vacuum distillation. The compounds prepared are detailed in Table II.

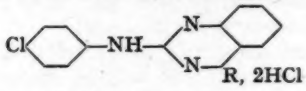
2-Chloro-4-hydroxyquinazoline (VI; R = OH).—2 : 4-Dichloroquinazoline (19·9 g.) (finely ground) and 2N-sodium hydroxide (150 c.c.) were stirred for 3 hours. After dilution with water (100 c.c.) and stirring for a further 10 minutes the solution was filtered from a little insoluble residue and the filtrate acidified with acetic acid. The precipitated product was filtered off, washed with water, and dried. Crystallised from alcohol it formed colourless needles, m. p. 218—220° (Found: C, 53·5; H, 2·95; Cl, 19·3. Calc. for $C_8H_5ON_2Cl$: C, 53·2; H, 2·8; Cl, 19·7%).

2-p-*Chloroanilino-4-hydroxyquinazoline* (VII; R = Cl, R′ = OH).—2-Chloro-4-hydroxyquinazoline (4·5 g.), *p*-chloroaniline (3·2 g.), water (30 c.c.), acetone (15 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were

TABLE I.

Antimalarial Activities.

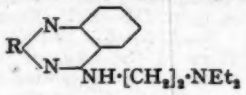
(*a*) 2-*p*-Chloroanilino-4-aminoalkylaminoquinazoline dihydrochlorides.



Reference No.	Nature of R.	Dose mg./kg.	Antimalaria activity.
3756	$NH\cdot[CH_2]_2\cdot NEt_2$	40	+ to ++
		20	±
3666	$NH\cdot[CH_2]_3\cdot NEt_2$ [1]	80	++
		40	+
		20	—
3915	$NH\cdot[CH_2]_4\cdot NEt_2$	160	+ to ++
		80	+
4248	$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$	80	+
		40	+
4087	$NMe\cdot[CH_2]_2\cdot NEt_2$	160	—
		80	—
		40	—
5155	$NMe\cdot[CH_2]_3\cdot NHMe$	160	++
		80	—
3933	$NH\cdot[CH_2]_2\cdot NMe_2$	80	+ to ++
		40	—
3979	$NH\cdot[CH_2]_3\cdot NMe_2$	80	++
		40	++
		20	+
4601	$NH\cdot[CH_2]_4\cdot NMe_2$	40	++
		20	+
4870	$NH\cdot[CH_2]_5\cdot NMe_2$	80	++
		40	+ to ++
		20	±
4869	$NH\cdot[CH_2]_6\cdot NMe_2$	80	+
		40	—
4626	$NH\cdot[CH_2]_3\cdot NMePr^{\beta}$	80	++
		40	+
4214	$NH\cdot[CH_2]_2\cdot NHBu^{\alpha}$	160	++
		40	+
4524	$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	80	++
		40	+
4589	$NH\cdot[CH_2]_4\cdot NBu^{\alpha}_2$	120	+ to ++
		80	+
4252	$NH\cdot[CH_2]_2\cdot N<[CH_2]_5>CH_2$	80	+
		40	±
4251	$NH\cdot[CH_2]_2\cdot N<[CH_2]_4>CH_2$	80	+
		40	—
3932	$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	80	++
		40	+
4575	$NH\cdot CHMe\cdot CH_2\cdot N<[CH_2]_4>CH_2$	160	++
		80	±
		40	—
4600	$NH\cdot CH_2\cdot CHMe\cdot N<[CH_2]_4>CH_2$	80	+
		40	±
4139	$NH\cdot[CH_2]_2\cdot NH_2$	120	+
		80	+
4496	$NH\cdot[CH_2]_2\cdot NHAc$	320	++
		80	—
4625	$NH\cdot[CH_2]_6\cdot NH_2$	160	+ to ++
		80	—
4608	$NH\cdot[CH_2]_3\cdot NMe\cdot[CH_2]_2\cdot NEt_2$ [2]	120	+
		80	±
		40	—

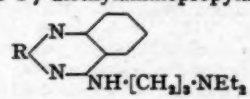
TABLE I—*contd.*

(*b*) 2-Arylamino-4-β-diethylaminoethylaminoquinazolines.



Reference No.	Nature of R.	Dose mg./kg.	Antimalarial activity.
3909	4-Methylthioanilino- [3]	80	++
		40	+
4086	*N*-Ethylanilino-	160	—
		80	—
		40	—
3761	2-Naphthylamino-	120	++
		80	+
		40	+
4103	6-Bromo-2-naphthylamino- [3]	80	+
		40	+
		20	—
4058	4 : 8-Dichloro-2-naphthylamino [3]	200	+
		120	±
		80	—
5131	4-Nitroanilino- [3]	80	++
		40	—

(*c*) 2-Arylamino-4-γ-diethylaminopropylaminoquinazolines.



3715	4-Anisidino-	80	++
		40	—
3758	Anilino-	80	+
3760	4-Toluidino-	80	++
		40	+
3757	2-Naphthylamino-	80	+
		40	+

(*d*) Miscellaneous quinazolines.

3975	2-Chloro-4-β-diethylaminoethylamino-	200	—
		120	—
		80	—
3690	2 : 4-Bis-(γ-diethylaminopropylamino)-	200	++

[1] Free base tested. [2] Trihydriodide. [3] Dihydrochloride.

TABLE II.

2-Chloro-4-aminoalkylaminoquinazolines (V).

R.	M.p.	Formula.	Analysis. Found, %.	Required, %.
$NH\cdot[CH_2]_2\cdot NMe_2$	96—98°	$C_{12}H_{15}N_4Cl$	Cl, 13·8	Cl, 14·2
$NH\cdot[CH_2]_3\cdot NMe_2$	74	$C_{13}H_{17}N_4Cl,2H_2O$	C, 51·8; H, 6·8; N, 18·7; Cl, 11·7	C, 51·8; H, 7·0; N, 18·6; Cl, 11·8
$NH\cdot[CH_2]_2\cdot NEt_2$	85 b. p. 185°/ 0·04 mm.	$C_{14}H_{19}N_4Cl$	C, 60·1; H, 6·8; Cl, 12·4	C, 60·3; H, 6·8; Cl, 12·75
	80—81	$C_{14}H_{19}N_4Cl,H_2O$	C, 56·8; H, 6·8; N, 18·9; Cl, 12·1	C, 56·7; H, 7·1; N, 18·9; Cl, 12·0
	202—203	$C_{14}H_{19}N_4Cl,HCl$ *	C, 53·6; H, 6·6; N, 17·9; Cl′, 10·9	C, 53·3; H, 6·35; N, 17·8; Cl′, 11·3
$NH\cdot[CH_2]_3\cdot NEt_2$	66—68	$C_{15}H_{21}N_4Cl,2H_2O$	N, 17·0	N, 17·0
$NH\cdot[CH_2]_4\cdot NEt_2$	71	$C_{16}H_{23}N_4Cl,H_2O$	N, 17·1; Cl, 11·3	N, 17·3; Cl, 10·9
$NH\cdot CHMe\cdot[CH_2]_2\cdot NEt_2$	oil, b. p. 200—203°/ 0·08 mm.	$C_{17}H_{25}N_4Cl$	N, 17·8	N, 17·5
$NMe\cdot[CH_2]_2\cdot NEt_2$	indefinite	$C_{15}H_{21}N_4Cl,3H_2O$	N, 16·5	N, 16·2
$NH\cdot[CH_2]_2\cdot N<[CH_2]_4>CH_2$	141	$C_{14}H_{21}N_4Cl,H_2O$	N, 17·3	N, 17·35
$NH\cdot[CH_2]_2\cdot NHAc$	206—207	$C_{12}H_{15}ON_4Cl$	Cl, 13·7	Cl, 13·4
$NH\cdot[CH_2]_2\cdot OH$	186	$C_{10}H_{10}ON_3Cl$	Cl, 15·6	Cl, 15·9

* Crystallised from aqueous hydrochloric acid.

refluxed for 1 hour. After cooling, the product was filtered off and washed with water. The *hydrochloride* was then dissolved in hot 2-ethoxyethanol, and the solution was made alkaline with ammonia and poured into water. The precipitated *base* was filtered off, dried, and crystallised from 2-ethoxyethanol; small colourless needles, m. p. 280—282° (Found: C, 61·9; H, 3·7; N, 15·4; Cl, 13·1. $C_{14}H_{10}ON_3Cl$ requires C, 61·9; H, 3·7; N, 15·5; Cl, 13·1%). The hydrochloride, which was also obtained by precipitation from a solution of the base in sodium hydroxide by the addition of hydrochloric acid, crystallised from 2-ethoxyethanol containing a little hydrochloric acid as colourless laminæ, m. p. 277° (Found: Cl, 23·2. $C_{14}H_{10}ON_3Cl,HCl$ requires Cl, 23·05%).

2-p-*Anisidino-4-hydroxyquinazoline* (VII; R = OMe, R′ = OH), prepared by the method given above for the corresponding *p*-chloroanilino-compound, crystallised from 2-ethoxyethanol in colourless thin prisms, m. p. 262—263° (Found: N, 16·1. $C_{15}H_{13}O_2N_3$ requires N, 15·7%).

4-*Chloro*-2-p-*chloroanilinoquinazoline* (VII; R = R′ = Cl).—2-*p*-Chloroanilino-4-hydroxyquinazoline (7·5 g.), phosphoryl chloride (30 c.c.), and dimethylaniline (5 c.c.) were refluxed for ½ hour and the mixture poured on ice (300 g.) and sodium hydroxide solution (100 c.c. of 32%). The precipitated solid was filtered off, washed alkali-free with cold water, and dried in a vacuum. The crude material was extracted with boiling chloroform, and the extract evaporated to small bulk and allowed to crystallise. Collected and recrystallised from chloroform the *product* formed colourless needles, m. p. 177—178° (Found: Cl, 25·0. $C_{14}H_9N_3Cl_2$ requires Cl, 24·5%).

4-Chloro-2-*p*-anisidinoquinazoline (VII; R = OMe, R′ = Cl), prepared in a similar manner from 2-*p*-anisidino-4-hydroxyquinazoline, was not isolated from the crude material but treated directly with γ-diethylaminopropylamine.

2 : 4-*Bis*-p-*chloroanilinoquinazoline*.—2 : 4-Dichloroquinazoline (3·6 g.) and *p*-chloroaniline (18 g.) were heated at 140° for 3 hours. The cooled melt was thoroughly extracted with dilute hydrochloric acid to remove *p*-chloroaniline, the insoluble hydrochloride dissolved in alcoholic sodium hydroxide, and the solution diluted with water. The precipitated product was collected, washed with water, and crystallised from alcohol, giving the *quinazoline* as a practically colourless microcrystalline powder, m. p. 185° (Found: Cl, 18·9. $C_{20}H_{14}N_4Cl_2$ requires Cl, 18·65%). The same compound was obtained by interaction of 4-chloro-2-*p*-chloroanilinoquinazoline with *p*-chloroaniline under similar conditions.

2-p-*Chloroanilino-4-ethoxyquinazoline* (VII; R = Cl, R′ = OEt).—2-Chloro-4-ethoxyquinazoline (20·85 g.) and *p*-chloroaniline (12·8 g.) in alcohol (200 c.c.) were refluxed for 1 hour. The clear solution was cooled and poured into sodium carbonate solution (800 c.c. of 2·5%). The *quinazoline* was precipitated as an oil which solidified on standing. It was filtered off, washed with water, and crystallised from alcohol (yield, 23·5 g.); glistening white laminæ, m. p. 122° (Found: Cl, 12·1. $C_{16}H_{14}ON_3Cl$ requires Cl, 11·85%). The hydrochloride separated as faintly yellow prisms, m. p. 175°, on adding hydrochloric acid to a solution of the base in alcohol.

Hydrolysis of 2-p-*Chloroanilino-4-ethoxyquinazoline*.—2-*p*-Chloroanilino-4-ethoxyquinazoline (1 g.), hydrochloric acid (5 c.c.), and water (10 c.c.) were refluxed for 5 hours. The product which separated on cooling was filtered off, dissolved in 0·5N-sodium hydroxide, the solution filtered, and hydrochloric acid added. The resulting hydrochloride was dissolved in 2-ethoxyethanol, and the solution was made alkaline with ammonia and diluted with water. The precipitated product was filtered off, dried, and crystallised from 2-ethoxyethanol, giving 2-*p*-chloroanilino-4-hydroxyquinazoline, m. p. and mixed m. p. 280—282°.

2-p-*Chloroanilino-4-phenoxyquinazoline* (VII; R = Cl, R′ = OPh).—2-Chloro-4-phenoxyquinazoline (6·4 g.), *p*-chloroaniline (3·2 g.), and alcohol (30 c.c.) were boiled under reflux for 1 hour. The product began to separate as a mass of crystals after ½ hour. The mixture was poured into sodium carbonate solution (200 c.c. of 2·5%), and the precipitated product filtered off and washed with water. The *quinazoline* was separated from a high-melting product by extraction with glacial acetic acid and reprecipitation with water. It then crystallised from alcohol as long colourless felted needles (yield, 2·5 g.), m. p. 186—187° (Found: Cl, 10·0. $C_{20}H_{14}ON_3Cl$ requires Cl, 10·2%).

2-*Chloro-4-methylthioquinazoline* (VI; R = SMe).—Methylthiol was passed into a cooled solution of sodium (2·5 g.) in alcohol (40 c.c.) until it was present in excess. The solution was diluted with alcohol (40 c.c.) and shaken with finely powdered 2 : 4-dichloroquinazoline (19·9 g.) with ice–water cooling until no further heat evolution occurred. After 16 hours at laboratory temperature the mixture was diluted with water (800 c.c.), allowed to stand for 1 hour, and the solid filtered off and dried. The *quinazoline* separated from light petroleum (b. p. 60—80°) as long colourless prisms, m. p. 122° (Found: N, 13·1. $C_9H_7N_3ClS$ requires N, 13·3%).

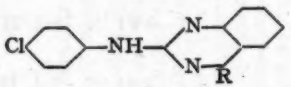
2-p-*Chloroanilino-4-methylthioquinazoline* (VII; R = Cl, R′ = SMe).—A solution of 2-chloro-4-methylthioquinazoline (5·26 g.) and *p*-chloroaniline (3·2 g.) in alcohol (50 c.c.) was refluxed for ½ hour. After a short time a felted mass of needles separated. The mixture was poured into sodium carbonate solution (200 c.c. of 2·5%), allowed to stand for some hours, and the product then filtered off. The *quinazoline* crystallised from alcohol as colourless needles, m. p. 176° (Found: S, 10·7. $C_{15}H_{12}N_3ClS$ requires S, 10·6%).

Preparation of 2-Arylamino-4-aminoalkylaminoquinazolines.—The methods used are illustrated by the following typical preparations. Details of the substances prepared are given in Tables III, IV, and V.

Method (*a*). 4-Chloro-2-*p*-chloroanilinoquinazoline (1·2 g.), β-diethylaminoethylamine (1 c.c.), and glacial acetic acid (5 c.c.) were heated at 95—100° for 1·5 hours; the mixture was then diluted with water (20 c.c.), boiled, and filtered from insoluble material. The filtrate was treated with hydrochloric acid (5 c.c.); 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride crystallised out on standing as colourless needles, m. p. 252—254°.

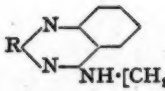
Method (*b*). 2-Chloro-4-β-diethylaminoethylaminoquinazoline (11·15 g., 0·04 g.-mol.), *p*-chloroaniline (10·5 g., 0·08 g.-mol.), and acetic acid (20 c.c.) were refluxed for 2 hours, and the solution cooled and poured into water (200 c.c.). Acet-*p*-chloroanilide (6 g.) separated and was filtered off. The filtrate was made alkaline with sodium hydroxide and steam distilled to remove *p*-chloroaniline. The gummy non-volatile base was separated, washed with water by decantation, and dissolved in 5% acetic acid (200 c.c.). The solution was treated with decolorising carbon and filtered, and hydrochloric acid (100

TABLE III.

2-p-*Chloroanilino-4-aminoalkylaminoquinazolines*, 

R.	Formula.	Method of preparation.	M. p.	Analysis. Found, %.	Analysis. Required, %.
$NH\cdot[CH_2]_2\cdot NH_2$	$C_{16}H_{16}N_5Cl$	*d*	142°	—	—
	$C_{16}H_{16}N_5Cl,2HCl,1{\cdot}5H_2O$	—	314—316	C, 46·5; H, 5·8; N, 17·4	C, 46·4; H, 5·1; N, 16·95
$NH\cdot[CH_2]_6\cdot NH_2$	$C_{20}H_{24}N_5Cl,2HCl,H_2O$	*d*	261—263	C, 51·7; H, 5·9; N, 15·0; Cl, 23·4; Cl′, 15·4	C, 52·0; H, 6·1; N, 15·2; Cl, 23·1; Cl′, 15·45
$NH\cdot[CH_2]_2\cdot NMe_2$	$C_{16}H_{20}N_5Cl,2HCl,2{\cdot}5H_2O$	*b, c*	267—268	C, 47·1; H, 5·45; N, 15·5	C, 47·05; H, 5·9; N, 15·25
$NH\cdot[CH_2]_3\cdot NMe_2$	$C_{19}H_{22}N_5Cl,2HCl,1{\cdot}5H_2O$	*b*	256—258	C, 50·2; H, 6·0; N, 15·6	C, 50·0; H, 5·9; N, 15·4
$NH\cdot[CH_2]_4\cdot NMe_2$	$C_{20}H_{24}N_5Cl,2HCl,H_2O$	*d*	261	C, 52·3; H, 5·5; N, 15·3; Cl′, 15·8	C, 52·05; H, 6·05; N, 15·2; Cl′, 15·4
$NH\cdot[CH_2]_5\cdot NMe_2$	$C_{21}H_{26}N_5Cl,2HCl,1{\cdot}5H_2O$	*d*	278	C, 52·3; H, 6·6; N, 14·7; Cl′, 14·4	C, 52·2; H, 6·4; N, 14·5; Cl′, 14·7
$NH\cdot[CH_2]_6\cdot NMe_2$	$C_{22}H_{28}N_5Cl,2HCl,1{\cdot}5H_2O$	*d*	156—158 (solidifies and remelts at 236°)	C, 53·0; H, 6·2; Cl′, 14·2	C, 53·0; H, 6·6; Cl′, 14·3
$NH\cdot[CH_2]_2\cdot NEt_2$	$C_{20}H_{24}N_5Cl$	*a, b, c, d*	111—112	C, 65·0; H, 6·4; N, 19·0	C, 65·0; H, 6·5; N, 18·95
	$C_{20}H_{24}N_5Cl,2HCl,2H_2O$	—	253—254	C, 50·5; H, 6·3; N, 14·3	C, 50·2; H, 6·3; N, 14·6
(Mono-acetyl derivative)	$C_{22}H_{26}ON_5Cl,2HCl$	—	248—249	Cl, 21·5; Cl′, 14·5	Cl, 21·9; Cl,′ 14·6
$NH\cdot[CH_2]_3\cdot NEt_2$	$C_{21}H_{26}N_5Cl,0{\cdot}5H_2O$	*a*	126—127	C, 64·2, 64·2; H, 6·8, 6·8; N, 17·9; Cl, 9·1	C, 64·2; H, 6·9; N, 17·85; Cl, 9·0
	$C_{21}H_{26}N_5Cl,2HCl,2H_2O$	—	274	Cl′, 14·2; Cl, 22·1	Cl′, 14·4; Cl, 21·6
$NH\cdot[CH_2]_4\cdot NEt_2$	$C_{23}H_{28}N_5Cl,2HCl,H_2O$	*b*	260—262	C, 53·9; H, 6·6; N, 14·0	C, 54·1; H, 6·55; N, 14·3
$NH\cdot CHMe\cdot[CH_2]_3\cdot NEt_2$	$C_{22}H_{30}N_5Cl,2HCl,2H_2O$	*d*	122 (solidifies and remelts at 205°)	C, 52·8; H, 7·0; N, 13·2; loss on drying, 7·0	C, 52·9; H, 6·9; N, 13·45; $2H_2O$, 6·9
$NH\cdot[CH_2]_3\cdot NMePr^{\beta}$	$C_{21}H_{26}N_5Cl,2HCl,2H_2O$	*d*	268—269	C, 51·2; H, 6·3; N, 14·2; Cl′, 14·8	C, 51·2; H, 6·5; N, 14·2; Cl′, 14·4
$NH\cdot[CH_2]_3\cdot NHBu^{\alpha}$	$C_{21}H_{26}N_5Cl,2HCl,H_2O$	*b, d*	254—256	C, 53·5; H, 6·8; N, 15·1	C, 53·2; H, 6·3; N, 14·75
$NH\cdot[CH_2]_3\cdot NBu^{\alpha}_2$	$C_{25}H_{34}N_5Cl,2HCl,0{\cdot}5H_2O$	*d*	193—194	C, 57·0; H, 7·4; N, 13·7; Cl′, 12·9	C 57·5; H, 6·7; N, 13·45; Cl′, 13·6
$NH\cdot[CH_2]_4\cdot NBu^{\alpha}_2$	$C_{26}H_{36}N_5Cl,2HCl,2H_2O$	*d*	181 (sinters at 151—152°)	C, 55·6; H, 6·9; N, 13·3; Cl′, 12·5	C, 55·45; H, 7·45; N, 12·45; Cl′, 12·65
$NH\cdot[CH_2]_2\cdot N<[CH_2]_3>CH_2$	$C_{20}H_{22}N_5Cl,2HCl,2{\cdot}5H_2O$	*d*	283—285	C, 49·1; H, 5·9; N, 14·5; Cl′, 15·3	C, 49·4; H, 6·0; N, 14·4; Cl′, 14·6
$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	$C_{21}H_{24}N_5Cl,2HCl,0{\cdot}5H_2O$	*d*	276—278	C, 54·2; H, 5·6; N, 14·7; Cl′, 15·0	C, 54·3; H, 5·8; N, 15·1; Cl′, 15·35
$NH\cdot[CH_2]_3\cdot N<[CH_2]_4>CH_2$	$C_{22}H_{26}N_5Cl,2HCl,0{\cdot}5H_2O$	*b, c*	285—286	C, 54·8; H, 6·4; N, 14·9	C, 55·3; H, 6·1; N, 14·7
$NH\cdot CHMe\cdot CH_2\cdot N<[CH_2]_4>CH_2$	$C_{23}H_{28}N_5Cl,2HCl,3H_2O$	*d*	274—275	C, 50·4; H, 6·3; N, 13·3; Cl′, 14·8	C, 50·45; H, 6·5; N, 13·4; Cl′, 13·6
$NH\cdot CH_2\cdot CHMe\cdot N<[CH_2]_4>CH_2$	$C_{23}H_{28}N_5Cl,2HCl,H_2O$	*d*	283—286	C, 54·4; H, 5·8; N, 14·7; Cl′, 14·7	C, 54·3; H, 6·15; N, 14·4; Cl′, 14·6
$NH\cdot[CH_2]_3\cdot NMe\cdot[CH_2]_2\cdot NEt_2$	$C_{24}H_{33}N_6Cl,3HI,2H_2O$	*d*	229	C, 32·9; H, 4·6; N, 9·8; I, 44·2	C, 33·5; H, 4·65; N, 9·8; I, 44·3
$NMe\cdot[CH_2]_2\cdot NEt_2$	$C_{21}H_{26}N_5Cl,2H_2O$	*b*	76	C, 60·1; H, 7·1; N, 16·7	C, 60·0; H, 7·15; N, 16·7
$NMe\cdot[CH_2]_3\cdot NHMe$	$C_{19}H_{22}N_5Cl,2HCl,2{\cdot}5H_2O$	*d*	137—138	C, 47·9; H, 5·9; N, 14·8; Cl′, 15·0	C, 48·2; H, 6·1; N, 14·8; Cl′, 15·0
$NH\cdot[CH_2]_2\cdot NHAc$	$C_{18}H_{18}ON_5Cl$	*b*	183—184	C, 60·3; H, 5·0; N, 19·7	C, 60·7; H, 5·05; N, 19·7
$NH\cdot[CH_2]_2\cdot OH$	$C_{16}H_{13}ON_4Cl$	*b, d*	174	C, 61·0; H, 5·0; N, 17·6	C, 61·0; H, 4·8; N, 17·8
	$C_{16}H_{13}ON_4Cl,HCl,H_2O$	—	286—287	Cl, 19·0	Cl, 19·25

TABLE IV.

2-Arylamino-4-β-diethylaminoethylaminoquinazolines, 

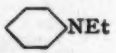
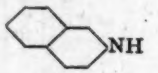
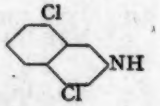
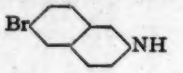
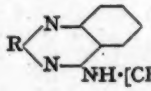
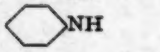
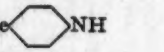
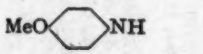
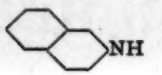
R.	Formula.	Method.	M. p.	Analysis. Found, %.	Required, %.
	$C_{21}H_{27}N_5S,2HCl,3H_2O$	*b*	130—131°	C, 49·3; H, 6·3; N, 13·8	C, 49·55; H, 6·9; N, 13·8
	$C_{20}H_{24}O_2N_6,2HCl,4H_2O$	*c*	286—287	C, 45·9; H, 4·8; N, 15·7; Cl′, 13·2	C, 45·7; H, 6·5; N, 16·0; Cl′, 13·5
	$C_{22}H_{29}N_5$	*b*	110	C, 72·7; H, 7·5; N, 19·3	C, 72·7; H, 8·0; N, 19·3
	$C_{24}H_{27}N_5$	*b*	126	C, 74·6; H, 6·8; N, 18·1	C, 74·75; H, 7·0; N, 18·2
	$C_{24}H_{25}N_5Cl_2,2HCl,H_2O$	*b*	284	C, 52·3; H, 5·3; N, 13·0	C, 52·8; H, 5·3; N, 12·85
	$C_{24}H_{26}N_5Br,2HCl,2H_2O$	*b*	284—285	C, 50·4; H, 5·8; N, 12·9	C, 50·25; H, 5·6; N, 12·25

TABLE V.

2-Arylamino-4-γ-diethylaminopropylaminoquinazolines, 

R.	Formula.	Method.	M. p.	Analysis. Found, %.	Required, %.
	$C_{21}H_{27}N_5$	*b*	112—114°	C, 72·0; H, 7·4; N, 19·9	C, 72·2; H, 7·7; N, 20·1
	$C_{22}H_{29}N_5$	*b*	94	C, 72·9; H, 7·8; N, 18·8	C, 72·7; H, 8·0; N, 19·3
	$C_{22}H_{29}ON_5$	*a*, *b*	114—115	C, 69·3; H, 7·4; N, 18·5	C, 69·7; H, 7·65; N, 18·5
	$C_{25}H_{29}N_5$		141	C, 75·2; H, 7·3; N, 17·2	C, 75·2; H, 7·25; N, 17·55

c.c.) added to the filtrate. 2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride crystallised out. It was filtered off and recrystallised from water (yield, 11·5 g.).

Methods (*a*) and (*b*) were varied by carrying out the reaction at 130—140° for 3 hours in the absence of acetic acid.

Method (*c*). 2-Chloro-4-β-diethylaminoethylaminoquinazoline (11·15 g., 0·04 g.-mol.), *p*-chloroaniline hydrochloride (6·6 g., 0·04 g.-mol.), water (40 c.c.), and 10N-hydrochloric acid (0·2 c.c.) were refluxed for 1 hour. On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated and was collected and recrystallised from water (yield, 10 g.).

Method (*d*). 2-*p*-Chloroanilino-4-ethoxyquinazoline (2·99 g., 0·01 g.-mol.) and β-diethylaminoethylamine (2·32 g., 0·02 g.-mol.) were heated under reflux at 140—150° for 2 hours. The cooled mixture was dissolved in acetic acid (10 c.c.), diluted with water (100 c.c.), and the solution boiled and filtered from a trace of insoluble matter. The filtrate was treated with hydrochloric acid (50 c.c.). On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated; it was filtered off and recrystallised from water (yield, 4 g.). In some cases, *e.g.*, with δ-diethylamino-α-methylbutylamine and β-piperidino*iso*propylamine, a higher reaction temperature (180—190°) was found to be necessary.

Condensation of 2-p-*Chloroanilino-4-phenoxyquinazoline and β-Diethylaminoethylamine.*—2-*p*-Chloroanilino-4-phenoxyquinazoline (1 g.) and β-diethylaminoethylamine (1·5 g.) were mixed and heated at 140—150° for 2·5 hours. The cooled mixture was treated with 5% sodium hydroxide (10 c.c.), the oil extracted with ether, and the ether solution washed with sodium hydroxide and then with water. It was then extracted with 5% acetic acid (15 c.c.), and the acetic acid extract separated and treated with hydrochloric acid (5 c.c.). 2-*p*-Chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated and was filtered off and dried; m. p. and mixed m. p. 253—254° (see Table III) (yield, 0·9 g.).

Condensation of 2-p-*Chloroanilino-4-methylthioquinazoline and β-Diethylaminoethylamine.*—2-*p*-Chloroanilino-4-methylthioquinazoline (3·75 g.) and a large excess of β-diethylaminoethylamine were boiled under reflux for 6 hours. The cooled mixture was extracted with hot 5% acetic acid, and the solution filtered and treated with hydrochloric acid. On cooling, 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride separated, m. p. and mixed m. p. 253°.

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152. *Synthetic Antimalarials. Part XV. Some Aryloxy- and Arylthio-dialkylaminoalkylaminopyrimidines.*

By F. H. S. CURD, (MISS) M. I. DAVIS, E. HOGGARTH, and F. L. ROSE.

The preparation of a number of 2(or 4)-dialkylaminoalkylamino-4(or 2)-aryloxy- and -arylthio-6-methylpyrimidines related to the 2-arylamino-4-dialkylaminoalkylamino- and -4-arylamino-2-dialkylaminoalkylamino-6-methylpyrimidines of previous papers in this series (*J.*, 1946, 343, 351, 370, 720) is described. Some of these new compounds show low antimalarial activity, and the theoretical implications of this are discussed.

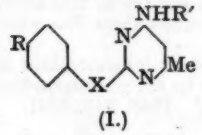
The 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines prepared as intermediates in the synthesis of compounds of type (I; X = S, O) afford a further route to the corresponding 2-arylamino-derivatives (I; X = NH) first described in Parts I and II (*J.*, 1946, 343, 351).

IN our original plan of work following the discovery of antimalarial activity in 2-arylamino-4-aminoalkylamino-6-methylpyrimidines such as (I; R = Cl, R′ = $[CH_2]_2 \cdot NEt_2$, X = NH), it was proposed to prepare compounds in which the imino-linkage between the aryl and the pyrimidine nucleus was replaced by other groups. In Part IV (Curd and Rose, *J.*, 1946, 362) the first step in this direction, the replacement of the imino-group by guanidino-, was described. The present communication deals with the preparation of compounds in which the conjugate grouping is a sulphide or ether linkage (*e.g.*, I; R′ = dialkylaminoalkyl, X = S or O). Since the compounds were also required for other chemotherapeutic investigations we have also prepared position isomers of this type, namely (II; X = S or O) analogous to the active 4-arylamino-2-aminoalkylamino-6-methylpyrimidines (II; X = NH) (Part VI; *J.*, 1946, 370; Part IX, *ibid.*, p. 720) and (III; X = S) corresponding to the inactive 4-arylamino-6-aminoalkylamino-2-methylpyrimidines (III; X = NH) (see Part VIII, *J.*, 1946, 713).

The interbond angle of imino-nitrogen is sufficiently close to those of oxygen and sulphur (with the greater divergence in the latter instance) to permit the formulation of molecules bearing a formal structural resemblance to riboflavin, and the possibility existed that they might be effective antimalarial agents on that account (cf. Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 157). The new compounds were, however, primarily intended to throw light on the types of linking group necessary to promote antimalarial activity. The activity of types [I; X = NH or NH·C(:NH)·NH] and (II; X = NH) contrasted with the inactivity of compounds analogous to (I) in which the aryl group is attached directly to the pyrimidine nucleus (see Part I, *loc. cit.*) had earlier suggested that a linking group capable of forming a prototropic system with the pyrimidine nucleus was necessary.

In later communications (Part X, *J.*, 1946, 729; Part XII, this vol., p. 154) these theoretical arguments have been developed, largely as a result of the positive activity of types (I and II; X = NH) as compared with the lack of antimalarial action in type (III; X = NH) and the corresponding 1 : 3 : 5-triazine series, and the working hypothesis developed that marked therapeutic effect, *in the molecular species under discussion*, was dependent upon the existence within the molecule of aryl and alkyl groups linked by a conjugated chain made up of alternating nitrogen and carbon atoms. In order to demonstrate such a conjugated path within the molecule it was frequently essential either to formulate the drug molecules in the tautomeric form of that conventionally used by supposing a prototropic shift (compare I; X = NH and Ib), or to postulate a major contribution to a resonance hybrid of an excited state such as (Ia and IIa), but we were not prepared to indicate which might be the more important factor. Now it was evident that sulphide and ether linkages could not provide for prototropic changes analogous to that of (I; X = NH) ⟶ (Ib), except in the unlikely event of sulphonium or oxonium salt formation, so that the slight but undoubted activity observed in certain compounds of types (I and II; X = S) (see table) would appear to lend some support to the view that resonance features are predominantly important. The lower activity or complete inactivity of the compounds containing an oxygen linkage would suggest, if our views are correct, that the oxonium structures (Ia and IIa; X = O) must contribute less to the hybrid state of the molecules than the corresponding structures (Ia and IIa; X = S) and the latter in turn are less probable than the corresponding imino-types. This is in accord with the known order of O < S < N in the electropositive series.

The association of high antimalarial activity in compounds of types [I; X = NH or NH·C(:NH)·NH] and (II; X = NH) with the presence of a group such as halogen, nitro-, or cyano- in the para position of the aryl nucleus has previously been correlated with their powerful electron-attracting effect, although the exact significance of this was not understood. The observation now made that compounds of types (I and II; X = S) containing a methoxy group (R = OMe) possess higher antimalarial activity than those containing a chlorine substituent (R = Cl) suggests that the function of the substituent may be an influence on the resonance structure of the drug molecule. The electron donating (+ *T*) effect of the methoxy group will, by increasing electron availability at the sulphur atom, enhance the significance of structures such as (Ia and IIa; X = S), whereas the powerful inductive effect of the chlorine atom (− *I*) will operate to the disadvantage of such structures.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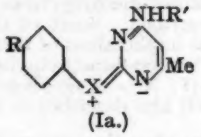
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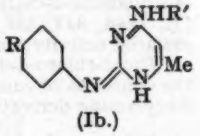
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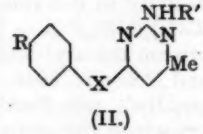
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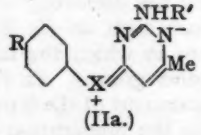
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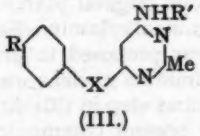
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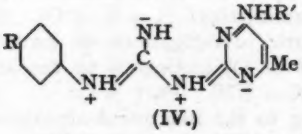
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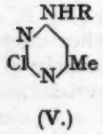
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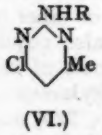
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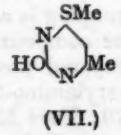
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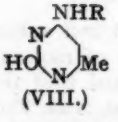
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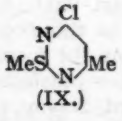
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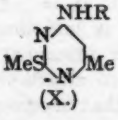
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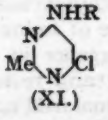
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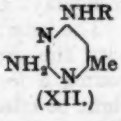
(XII.)

In addition to the views expressed above to account for the reduced activity of (I and II; X = S or O) as compared with (I and II; X = NH), it is desirable to consider a further factor which will operate in the same direction. The chemical lability of certain types of 2- or 4-alkylthiopyrimidines is well known, and we have demonstrated the anticipated greater lability of phenoxy- as opposed to anilino- by the reaction of 2-p-*chloroanilino*-4-*phenoxy*-6-*methylpyrimidine* with β-diethylaminoethylamine to give the corresponding 4-β-diethylaminoethyl-

amino-derivative and with γ-diethylaminopropylamine to give (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = NH). It is conceivable, therefore, that the thioether and ether drugs are much less stable *in vivo* than the drugs of the imino-type.

For the preparation of compounds of types (I and II; X = S), 2-chloro-4-aminoalkylamino-6-methylpyrimidines (V) and 4-chloro-2-aminoalkylamino-6-methylpyrimidines (VI) were required. Substances of type (VI) had been prepared previously (see Part VI, *loc. cit.*) and a method has now been developed for the preparation of those of type (V). It was first demonstrated that 2-hydroxy-4-methylthio-6-methylpyrimidine (VII) underwent reaction with dialkylaminoalkylamines such as β-diethylaminoethylamine, γ-diethylaminopropylamine, and δ-diethylamino-α-methylbutylamine to give 4-dialkylaminoalkylamino-2-hydroxy-6-methylpyrimidines (VIII) which on treatment with phosphoryl chloride were converted into the required 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V). The method was, however, an unattractive one as the preparation of the starting material (VII) involved a four stage synthesis from 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431). A more convenient method was provided by the following: 4-chloro-2-methylthio-6-methylpyrimidine (*idem*, *ibid.*) (IX) was brought into reaction with a dialkylaminoalkylamine to give a 4-dialkylaminoalkylamino-2-methylthio-6-methylpyrimidine (X) which was then hydrolysed to the corresponding 4-dialkylaminoalkylamino-2-hydroxy-6-methylpyrimidine (VIII) (isolated as dihydrochloride), which was in turn converted by treatment with phosphoryl chloride into the 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidine (V). Using this method the following were prepared: 2-*chloro*-4-β-*diethylaminoethylamino*- (V; R = $[CH_2]_3$·NEt_2), 2-*chloro*-4-γ-*diethylaminopropylamino*- (V; R = $[CH_2]_3$·NEt_2) and 2-*chloro*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (V; R = CHMe·$[CH_2]_3$·NEt_2).

These compounds of type (V) were then brought into reaction with thiophenols such as *p*-chlorothiophenol and *p*-methoxythiophenol, and a series of compounds of type (I; X = S) was thus obtained. Probably because of the intervention of side reactions attemps to condense the 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V) with sodium *p*-chloro- or *p*-methoxy-thiophenoxide in boiling alcoholic solution were unsatisfactory, although both methods were successfully used for the corresponding conversion of the 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidines (VI) into type (II; X = S).

Because of the greater activity found in type (II; X = S) than (I; X = S) the exploration of compounds containing an oxygen linkage was carried out mainly in type (II; X = O), and the only compound of type (I) containing an oxygen linkage made was 4-δ-*diethylamino*-α-*methylbutylamino*-2-p-*chlorophenoxy*-6-*methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O) by melting together *p*-chlorophenol and (V; R = CHMe·$[CH_2]_3$·NEt_2). Of the compounds of type (II; X = O), 2-δ-*diethylamino*-α-*methylbutylamino*-4-p-*chlorophenoxy*-6-*methylpyrimidine* (II; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O) resulted from the interaction of sodium *p*-chlorophenoxide with (VI; R = CHMe·$[CH_2]_3$·NEt_2) in alcoholic solution, while the sodium salt of quinol monomethyl ether melted with (VI; R = $[CH_2]_2$·NEt_2) gave 2-β-*diethylaminoethylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = O) and with (VI; R = $[CH_2]_3$·NEt_2) gave 2-γ-*diethylaminopropylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = O).

The 4-dialkylaminoalkylamino-6-*p*-chlorophenylthio-2-methylpyrimidines (III; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) and (III; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) were prepared by melting *p*-chlorothiophenol with, respectively, 4-chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (XI; R = $[CH_2]_3$·NEt_2) and 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (XI; R = CHMe·$[CH_2]_3$·NEt_2) which were available as the result of other work (forthcoming publication).

The discovery of a satisfactory method for the preparation of 2-chloro-4-dialkylaminoalkylamino-6-methylpyrimidines (V) (see above) opened up an alternative route for the preparation of compounds of type (I; X = NH). It was found that compounds of type (V) condensed with *p*-chloroaniline either at 150—160° (lower temperatures may be sufficient) or preferably in boiling aqueous solution as their monohydrochlorides in presence of a little extra hydrochloric acid as catalyst. Thus, 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = NH) (2666) was prepared from (V; R = $[CH_2]_2$·NEt_2) 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = NH) (3299) from (V; R = $[CH_2]_3$·NEt_2), and 2-*p*-chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = NH) (3300) from (V; R = CHMe·$[CH_2]_3$·NEt_2) (see Part I, *loc. cit.*). Similarly, by heating with alcoholic ammonia in a sealed tube at 180—200° (V; R = $[CH_2]_2$·NEt_2) was converted

into 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine (XII; R = $[CH_2]_2$·NEt_2), and (V; R = CHMe·$[CH_2]_3$·NEt_2) into 2-amino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (XII; R = CHMe·$[CH_2]_3$·NEt_2) (see Part III, *J.*, 1946, 357).

Table: Antimalarial Activities.

For interpretation of the results see Part I (*loc. cit.*).

Ref. No.	Pyrimidine.	Dose, mg./kg.	Activity.
5101	4-β-Diethylaminoethylamino-2-*p*-chlorophenylthio-6-methyl-	160	—
		80	—
5140	4-β-Diethylaminoethylamino-2-*p*-methoxyphenylthio-6-methyl	160	±
		80	—
5208	4-γ-Diethylaminopropylamino-2-*p*-chlorophenylthio-6-methyl-	160	—
5209	4-γ-Diethylaminopropylamino-2-*p*-methoxyphenylthio-6-methyl-	160	—
		80	—
5151	4-δ-Diethylamino-α-methylbutylamino-2-*p*-chlorophenylthio-6-methyl-	160	±
		80	—
5649	4-δ-Diethylamino-α-methylbutylamino-2-*p*-chlorophenoxy-6-methyl-	160	—
		80	—
4988	2-β-Diethylaminoethylamino-4-*p*-chlorophenylthio-6-methyl-	160	—
5019	2-β-Diethylaminoethylamino-4-*p*-methoxyphenylthio-6-methyl-	120	Toxic
		80	+
		40	+
5931	2-β-Diethylaminoethylamino-4-*p*-methoxyphenoxy-6-methyl-	160	—
		80	—
5037	2-γ-Diethylaminopropylamino-4-*p*-chlorophenylthio-6-methyl-	80	—
5020	2-γ-Diethylaminopropylamino-4-*p*-methoxyphenylthio-6-methyl-	80	+ to ++
		40	+
5932	2-γ-Diethylaminopropylamino-4-*p*-methoxyphenoxy-6-methyl-	160	+
		80	—
5045	2-δ-Diethylamino-α-methylbutylamino-4-*p*-chlorophenylthio-6-methyl-	160	Toxic
		80	—
5065	2-δ-Diethylamino-α-methylbutylamino-4-*p*-methoxyphenylthio-6-methyl-	160	+
		80	±
5150	2-δ-Diethylamino-α-methylbutylamino-4-*p*-chlorophenoxy-6-methyl-	160	Toxic
		80	—
5935	2-γ-Di-*n*-butylaminopropylamino-4-*p*-chlorophenylthio-6-methyl-	160	—
		80	—
5934	2-γ-Di-*n*-butylaminopropylamino-4-*p*-methoxyphenylthio-6-methyl-	160	—
		80	—
5342	4-γ-Diethylaminopropylamino-6-*p*-chlorophenylthio-2-methyl-	Not tested	
5727	4-δ-Diethylamino-α-methylbutylamino-6-*p*-chlorophenylthio-2-methyl-	Not tested	

Experimental.

4-β-Diethylaminoethylamino-2-methylthio-6-methylpyrimidine (X; R = $[CH_2]_2$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (17·45 g.) and β-diethylaminoethylamine (12·8 g.) were heated (oil-bath) to 80° and when the resulting reaction had subsided the temperature was gradually raised to 150° during 1 hour. The mixture was then cooled, treated with sodium hydroxide solution, and extracted with benzene. The dried (Na_2SO_4) benzene solution on evaporation left an oil which was purified by vacuum distillation to give the *pyrimidine* (12·5 g.), b. p. 150—151·5°/1·2 mm. (Found: S, 12·5. $C_{11}H_{23}N_4S$ requires S, 12·6%). On treatment with water it formed a *monohydrate* which crystallised from light petroleum (b. p. 60—80°) in colourless prisms (Found: C, 53·0; H, 8·6; S, 11·5. $C_{11}H_{23}N_4S,H_2O$ requires C, 52·9; H, 8·8; S, 11·8%). The *dipicrate* separated from alcohol in clumps of yellow prisms, m. p. 155—157° (Found: C, 40·6; H, 4·2; N, 19·3. $C_{11}H_{22}N_4S,2C_6H_3O_7N_3$ requires C, 40·45; H, 3·9; N, 19·7%).

4-β-Diethylaminoethylamino-2-hydroxy-6-methylpyrimidine (VIII; R = $[CH_2]_2$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (31 g.) and β-diethylaminoethylamine (23 g.) were heated at 160—170° for 2 hours. Crystallisation of the residue from chloroform–ethyl acetate gave the *product* as colourless prisms, m. p. 230—232° (Found: C, 56·7; H, 8·7; N, 24·7. $C_{11}H_{20}ON_4,0·5H_2O$ requires C, 56·7; H, 9·0; N, 24·0%). It formed a *dipicrate* which crystallised from 2-ethoxyethanol in yellow laminæ, m. p. 223—224° (Found: C, 40·0; H, 3·8; N, 20·4. $C_{11}H_{20}ON_4,2C_6H_3O_7N_3$ requires C, 40·5; H, 3·8; N, 20·5%).

(*b*) A solution of 4-β-diethylaminoethylamino-2-methylthio-6-methylpyrimidine (10 g.) in hydrochloric acid (100 c.c.) was boiled under reflux for 12 hours and the solution evaporated to dryness under reduced pressure. Crystallisation of the dried residual solid from alcohol gave *4-β-diethylaminoethylamino-2-hydroxy-6-methylpyrimidine dihydrochloride* as colourless needles, m. p. 258—260° (decomp.) (yield, 8·6 g.) (Found: C, 42·5; H, 7·4; N, 17·8. $C_{11}H_{20}ON_4,2HCl,H_2O$ requires C, 41·9; H, 7·6; N, 17·8%). This dihydrochloride was dissolved in water, and the solution exactly neutralised with sodium hydroxide solution and evaporated to dryness under reduced pressure. The product was extracted from the residue with chloroform, the solvent evaporated, and the material crystallised from alcohol–ethyl acetate; m. p. 230—232° (decomp.) (Found: C, 49·9; H, 7·9; N, 20·7. $C_{11}H_{20}ON_4,2H_2O$ requires C, 50·7; H, 7·9; N, 20·7%). It gave a dipicrate, m. p. 222—224° undepressed on admixture

with the picrate of the compound made by method (*a*). Probably because the substance formed different and indefinite hydrates, mixed melting point determinations were unsatisfactory for demonstrating the identity of the bases made by methods (*a*) and (*b*), but the evidence obtained from the identity of the picrates was substantiated by the identity of the chloropyrimidines prepared from the hydroxy-compound made by the two methods (see below).

2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (V; R = $[CH_2]_2$·NEt_2).—(*a*) 4-β-Diethylaminoethylamino-2-hydroxy-6-methylpyrimidine (40 g.), made by method (*a*) above, and phosphoryl chloride (60 c.c.) were refluxed for 2 hours. The mixture was cooled and poured on ice, and when the ice had melted the solution was made alkaline with sodium hydroxide. The liberated product was extracted with benzene and the solution dried (K_2CO_3). Distillation of the residue left after evaporation of the benzene gave the *pyrimidine* as a colourless oil, b. p. 144—146°/0·1 mm. (yield, 23·9 g.). On being stirred with water it formed a solid *hydrate* which crystallised from light petroleum (b. p. 60—80°); m. p. 55—56° (Found: N, 21·7; Cl, 12·9; loss on drying at 100°, 7·0. $C_{11}H_{19}N_4Cl,H_2O$ requires N, 21·5; Cl, 13·6; H_2O, 6·9%). The *dipicrate* crystallised from methanol in yellow prisms, m. p. 126—128° (Found: C, 39·4; H, 3·5; N, 19·4. $C_{11}H_{19}N_4Cl,2C_6H_3O_7N_3$ requires C, 39·4; H, 3·6; N, 20·0%).

(*b*) 4-β-Diethylaminoethylamino-4-hydroxy-6-methylpyrimidine dihydrochloride (52 g.), prepared by method (*b*) above, and phosphoryl chloride (500 c.c.) were refluxed until all the solid had dissolved (*ca.* 6 hours). The solution was then evaporated under reduced pressure to remove the excess of phosphoryl chloride and the residue poured on ice (1 kg.). Further working up was carried out as in (*a*) to give the chloropyrimidine, b. p. 160—162°/0·5 mm. (yield 50%) (Found: Cl, 14·2. $C_{11}H_{19}N_4Cl$ requires Cl, 14·6%). It gave a dipicrate, m. p. 126—128° undepressed by the dipicrate made from the compound obtained by method (*a*).

4-γ-Diethylaminopropylamino-2-methylthio-6-methylpyrimidine (X; R = $[CH_2]_3$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (17·4 g.) and γ-diethylaminopropylamine (13 g.) were heated under a wide condenser. At 85—90° a vigorous reaction took place. When this had subsided the mixture was heated at 130—140° for ½ hour. It was then cooled, sodium hydroxide solution added, and the product extracted with benzene. Evaporation of the dried benzene solution and distillation of the residue gave the *product* as a yellow oil, b. p. 168—170°/1 mm. (yield 20 g.) (Found: S, 11·7. $C_{13}H_{24}N_4S$ requires S, 11·9%). The *dipicrate* crystallised from alcohol in yellow prisms, m. p. 125—127° (Found: C, 41·6; H, 4·1; N, 19·7. $C_{13}H_{24}N_4S,2C_6H_3O_7N_3$ requires C, 41·3; H, 4·1; H, 19·3%).

4-γ-Diethylaminopropylamino-2-hydroxy-6-methylpyrimidine (VIII; R = $[CH_2]_3$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (5·2 g.) and γ-diethylaminopropylamine (4·9 g.) were heated at 150—160° for 3 hours. Crystallisation of the residue from chloroform–ethyl acetate gave the *pyrimidine* as colourless laminæ, m. p. 183—184° (Found: C, 60·2; H, 8·8; N, 22·8. $C_{12}H_{22}ON_4$ requires C, 60·5; H, 9·2; N, 23·5%).

(*b*) 4-γ-Diethylaminopropylamino-2-methylthio-6-methylpyrimidine (10 g.) and hydrochloric acid (100 c.c.) were refluxed for 24 hours. The solution was then evaporated to dryness under reduced pressure and the dried residue crystallised from alcohol, giving the *dihydrochloride* as colourless laminæ, m. p. 264—266° (yield, 9·5 g.) (Found: C, 46·3; H, 7·7; N, 18·0; Cl′, 22·1. $C_{12}H_{22}ON_4,2HCl$ requires C, 46·3; H, 7·7; N, 18·0; Cl′, 22·8%). The dihydrochloride (5 g.) was dissolved in water, and the solution neutralised with N-sodium hydroxide (33·15 c.c.) and evaporated to dryness under reduced pressure. After being dried by repeated evaporation to dryness with alcohol, the product was dissolved out with chloroform, the solution filtered, and ethyl acetate added. Crystallisation of the precipitated solid gave the base, m. p. 182—184° undepressed on admixture with that made from 2-hydroxy-4-methylthio-6-methylpyrimidine.

2-Chloro-4-γ-diethylaminopropylamino-6-methylpyrimidine (V; R = $[CH_2]_3$·NEt_2).—4-γ-Diethylaminopropylamino-2-hydroxy-6-methylpyrimidine dihydrochloride (62·5 g.) and phosphoryl chloride (500 c.c.) were refluxed for 8 hours. Excess of phosphoryl chloride was then removed under reduced pressure and the residue added to ice. The resulting solution was made alkaline with sodium hydroxide (cooling), the liberated oil extracted with benzene, and the solution dried (K_2CO_3). Evaporation gave the *pyrimidine* which was purified by vacuum distillation (b. p. 164—166°/0·9 mm.); it then set to a mass of crystals (yield, 26 g.) which separated from light petroleum (b. p. 40—60°); m. p. 45° (Found: C, 56·1; H, 8·1; Cl, 13·5. $C_{12}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 13·8%).

4-δ-Diethylamino-α-methylbutylamino-2-methylthio-6-methylpyrimidine (X; R = CHMe·$[CH_2]_3$·NEt_2).—4-Chloro-2-methylthio-6-methylpyrimidine (8·7 g.) and δ-diethylamino-α-methylbutylamine (17·4 g.) were gradually heated to 120°. At this temperature a vigorous reaction ensued, and when this had subsided the mixture was heated at 120—130° for 1 hour. It was then cooled, poured into water, and made alkaline with sodium hydroxide. The oily product was extracted with benzene and the extract dried and evaporated. Distillation of the residue gave the *pyrimidine*, b. p. 176—178°/0·9 mm. (yield, 8·8 g.) (Found: S, 11·0. $C_{15}H_{28}N_4S$ requires S, 10·8%).

4-δ-Diethylamino-α-methylbutylamino-2-hydroxy-6-methylpyrimidine (VIII; R = CHMe·$[CH_2]_3$·NEt_2).—(*a*) 2-Hydroxy-4-methylthio-6-methylpyrimidine (5·2 g.) and δ-diethylamino-α-methylbutylamine (5·3 g.) were heated in an oil-bath at 150—160° for 3 hours. The resulting mass was heated with benzene, cooled, and the insoluble material filtered off. Crystallisation from ethyl acetate gave the product as a *hemihydrate* of indefinite melting point (134—140°) (Found in material dried at 60—65°: C, 60·4; H, 9·6; N, 20·5. $C_{14}H_{26}ON_4,0·5H_2O$ requires C, 61·2; H, 9·8; N, 20·4%). It was slightly hygroscopic, and on storing turned to a sticky mass (Found in material dried in a vacuum at 80°: C, 62·7; H, 9·9; N, 20·9. $C_{14}H_{26}ON_4$ requires C, 63·2; H, 9·2; N, 21·1%). The *dipicrate* separated from 2-ethoxyethanol–alcohol in thick yellow prisms, m. p. 179—180° (Found: C, 43·0; H, 4·7; N, 19·6. $C_{14}H_{26}ON_4,2C_6H_3O_7N_3$ requires C, 43·1; H, 4·4; N, 19·3%).

(*b*) 4-δ-Diethylamino-α-methylbutylamino-2-methylthio-6-methylpyrimidine (10 g.) and hydrochloric acid (100 c.c.) were boiled under reflux for 24 hours. The solution was then evaporated to dryness under reduced pressure and the residue dried by repeated evaporation in the same way with alcohol and benzene. It was neither possible nor necessary to purify this hydrochloride for the preparation of 2-chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (see p. 788). To obtain

the base, a portion of the hydrochloride was dissolved in water, and the solution neutralised with the calculated quantity of N-sodium hydroxide solution and evaporated to dryness. The dried residue was extracted with chloroform, and the solution filtered and precipitated with ethyl acetate. On account of its hygroscopic nature no attempt was made to demonstrate the identity of the base with that made by method (*a*). Instead, it was converted into the dipicrate, m. p. 177—179° either alone or admixed with the picrate of the compound made by method (*a*).

2-Chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (V; R = CHMe·$[CH_2]_3$·NEt_2).—4-δ-Diethylamino-α-methylbutylamino-2-hydroxy-6-methylpyrimidine dihydrochloride (crude) (56·5 g.) and phosphoryl chloride (300 c.c.) were refluxed for 14 hours and the excess of phosphoryl chloride then removed under reduced pressure. The residue was poured on ice and the resulting solution made alkaline with sodium hydroxide, the solution being kept below 30° by addition of ice. The liberated base was extracted with benzene, and the extract dried and evaporated. Distillation of the residual oil gave the *pyrimidine*, b. p. 185—188°/1·2 mm. (yield, 34·5 g.) (Found: Cl, 12·2. $C_{14}H_{25}N_4Cl$ requires Cl, 12·5%).

4-β-Diethylaminoethylamino-2-p-chlorophenylthio-6-methylpyrimidine (I; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = S).—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (8 g.) and *p*-chlorothiophenol (9·6 g.) were heated in an oil-bath at 120° for 3 hours. Water (100 c.c.) and acetic acid (15 c.c.) were added, excess *p*-chlorothiophenol was removed by filtration, and the filtrate made strongly alkaline with sodium hydroxide solution. The oil was extracted with benzene, and the solution dried and evaporated. The residue was distilled to give the *pyrimidine* (yield, 10 g.) as a colourless oil, b. p. 202—204°/0·5 mm. (Found: Cl, 9·7; S, 9·1. $C_{17}H_{23}N_4ClS$ requires Cl, 10·1; S, 9·1%) which formed a *monohydrate*; colourless plates from light petroleum (b. p. 60—80°), m. p. 70° (Found: Cl, 9·5; S, 8·4. $C_{17}H_{23}N_4ClS,H_2O$ requires Cl, 9·65; S, 8·7%) (5101).

The following compounds were made in the same way. *4-β-Diethylaminoethylamino-2-p-methoxyphenylthio-6-methylpyrimidine* (I; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = S) was a pale yellow oil, b. p. 206—208°/1 mm., giving a *monohydrate* which crystallised from light petroleum (b. p. 60—80°); colourless prisms, m. p. 83° (Found: C, 59·7; H, 7·95; N, 16·2; S, 8·8; loss on drying in a vacuum at 100°, 4·9. $C_{18}H_{26}ON_4S,H_2O$ requires C, 59·3; H, 7·7; N, 15·4; S, 8·8; H_2O, 4·9%) (5140). *4-γ-Diethylaminopropylamino-2-p-chlorophenylthio-6-methylpyrimidine* (I; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 228—230°/2 mm. (Found: Cl, 9·8; S, 8·4. $C_{18}H_{25}N_4ClS$ requires Cl, 9·7; S, 8·8%) (5208). *4-γ-Diethylaminopropylamino-2-p-methoxyphenylthio-6-methylpyrimidine* (I; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = S) was a pale yellow oil, b. p. 228—229°/2 mm. (Found: C, 62·9; H, 7·9; N, 15·4; S, 8·8. $C_{19}H_{28}ON_4S$ requires C, 63·3; H, 7·8; N, 15·5; S, 8·9%) (5209). *4-δ-Diethylamino-α-methylbutylamino-2-p-chlorophenylthio-6-methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 208—210°/0·9 mm. (Found: C, 60·8; H, 7·0; Cl, 9·5; S, 8·1. $C_{20}H_{29}N_4ClS$ requires C, 61·2; H, 7·4; Cl, 9·05; S, 8·15%) (5151). *4-δ-Diethylamino-α-methylbutylamino-2-p-chlorophenoxy-6-methylpyrimidine* (I; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = O), prepared from 2-chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine and *p*-chlorophenol, was a pale yellow oil, b. p. 225—228°/0·1 mm. (Found: C, 63·6; H, 7·8; Cl, 9·7. $C_{20}H_{29}ON_4Cl$ requires C, 63·7; H, 7·7; Cl, 9·4%) (5649). *2-γ-Di-n-butylaminopropylamino-4-p-chlorophenylthio-6-methylpyrimidine* (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2, X = S), prepared from 4-chloro-2-γ-dibutylaminopropylamino-6-methylpyrimidine and *p*-chlorothiophenol, had b. p. 192—194°/0·08 mm., m. p. 59—60° (Found: C, 63·2; H, 7·7; N, 13·6; Cl, 8·3; S, 8·0. $C_{22}H_{33}N_4ClS$ requires C, 62·9; H, 7·8; N, 13·3; Cl, 8·4; S, 7·6%); with picric acid in methanol it gave a *dipicrate* which crystallised from 2-ethoxyethanol as yellow prisms, m. p. 151—152° (Found: C, 46·5; H, 4·7; N, 16·0. $C_{22}H_{33}N_4ClS,2C_6H_3O_7N_3$ requires C, 46·45; H, 4·4; N, 15·9%) (5935). *2-γ-Di-n-butylaminopropylamino-4-p-methoxyphenylthio-6-methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NBu^n_2, X = S), prepared from 4-chloro-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine and *p*-methoxythiophenol, was a very pale yellow oil, b. p. 202—204°/0·09 mm. (Found: C, 66·1; H, 8·4; N, 13·7; S, 7·3. $C_{23}H_{36}ON_4S$ requires C, 66·3; H, 8·7; N, 13·5; S, 7·7%); it gave a *dipicrate*, yellow prisms from 2-ethoxyethanol, m. p. 154—156° (Found: C, 48·1; H, 4·7; N, 15·7. $C_{23}H_{36}ON_4S,2C_6H_3O_7N_3$ requires C, 48·1; H, 4·8; N, 16·0%) (5934).

2-β-Diethylaminoethylamino-4-p-chlorophenylthio-6-methylpyrimidine (II; R = Cl, R′ = $[CH_2]_2$·NEt_2, X = S).—Sodium (5 g.) was dissolved in absolute alcohol (500 c.c.), *p*-chlorothiophenol (29 g.) followed by 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (48 g.) were added, and the mixture was refluxed for 8 hours. Water (500 c.c.) was added, the liquid made strongly alkaline with sodium hydroxide solution, and the oil extracted with benzene. The dried extract was evaporated and the residue distilled, giving a colourless oil (yield, 23 g.), b. p. 201—212°/0·1 mm., which set to a crystalline solid and then crystallised from light petroleum (b. p. 60—80°) in large rosettes of colourless needles, m. p. 83° (Found: Cl, 10·3; S, 9·0. $C_{17}H_{23}N_4ClS$ requires Cl, 10·1; S, 9·1%) (4988).

The following compounds were made in the same way. *2-β-Diethylaminoethylamino-4-p-methoxyphenylthio-6-methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_2$·NEt_2, X = S) had b. p. 212—214°/0·8 mm.; it crystallised from light petroleum (b. p. 80—100°) in clumps of colourless needles, m. p. 68—69° (Found: C, 62·3; H, 7·35; S, 9·3. $C_{18}H_{26}ON_4S$ requires C, 62·4; H, 7·5; S, 9·3%) (5019). *2-γ-Diethylaminopropylamino-4-p-chlorophenylthio-6-methylpyrimidine* (II; R = Cl, R′ = $[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 228—230°/0·7 mm., setting to a crystalline solid which crystallised from light petroleum (b. p. 80—100°) in large colourless plates, m. p. 83° (Found: C, 59·3; H, 6·9; Cl, 9·7; S, 8·8. $C_{18}H_{25}N_4ClS$ requires C, 59·3; H, 6·8; Cl, 9·7; S, 8·8%) (5037). *2-γ-Diethylaminopropylamino-4-p-methoxyphenylthio-6-methylpyrimidine* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2, X = S) had b. p. 228—230°/2 mm.; it separated from light petroleum (b. p. 80—100°) in large colourless prisms, m. p. 69—70° (Found: C, 63·1; H, 7·5; S, 9·0. $C_{19}H_{28}ON_4S$ requires C, 63·3; H, 7·8; S, 8·9%) (5020). *2-δ-Diethylamino-α-methylbutylamino-4-p-chlorophenylthio-6-methylpyrimidine* (II; R = Cl, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 224—226°/3 mm. (Found: Cl, 8·8; S, 8·3. $C_{20}H_{29}N_4ClS$ requires Cl, 9·05; S, 8·15%) (5045). *2-δ-Diethylamino-α-methylbutylamino-4-p-methoxyphenylthio-6-methylpyrimidine* (II; R = OMe, R′ = CHMe·$[CH_2]_3$·NEt_2, X = S) was a colourless oil, b. p. 210—212°/1·5 mm. (Found: C, 64·5; H, 7·9; S, 8·1. $C_{21}H_{32}ON_4S$ requires C, 65·0; H, 8·2;

S, 8·2%) (5065). 2-δ-*Diethylamino-α-methylbutylamino*-4-p-*chlorophenoxy*-6-*methylpyrimidine* (II; R = Cl, R′ = CHMe·[CH$_2$]$_3$·NEt$_2$, X = O), prepared from 4-chloro-2-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine and *p*-chlorophenol, was first obtained as a colourless oil, b. p. 190—193°/0·1 mm., which set to a crystalline solid, m. p. 42° (Found: C, 63·7; H, 7·9; Cl, 9·7. $C_{20}H_{29}ON_4Cl$ requires C, 63·7; H, 7·7; Cl, 9·4%) (5150).

2-β-*Diethylaminoethylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = [CH$_2$]$_2$·NEt$_2$, X = O).—Sodium (1·2 g.) was dissolved in alcohol (100 c.c.), quinol monomethyl ether (6·2 g.) added, and the solution evaporated to dryness under reduced pressure in an inert atmosphere. The residue was dried by evaporation twice with alcohol (10 c.c.) and then powdered in a mortar and added to 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (12·1 g.). The mixture was heated at 150° for 3 hours. The resulting melt was dissolved in acetic acid (50 c.c.) and the solution poured into water (250 c.c.). The clear solution was made alkaline with sodium hydroxide and extracted thrice with benzene. After being washed with water, the benzene solution was shaken twice with 25% acetic acid, the combined aqueous extracts were basified with sodium hydroxide, and the liberated oil was extracted with benzene. Evaporation of the dried benzene solution and distillation of the residue gave the *product*, b. p. 188—190°/0·05 mm., which solidified and then crystallised from light petroleum (b. p. 60—80°) as large colourless needles, m. p. 61° (Found: C, 65·0; H, 7·6. $C_{18}H_{28}O_2N_4$ requires C, 65·4; H, 7·9%) (5931).

2-γ-*Diethylaminopropylamino*-4-p-*methoxyphenoxy*-6-*methylpyrimidine* (II; R = OMe, R′ = [CH$_2$]$_3$·NEt$_2$, X = O) was prepared in a similar manner using 4-chloro-2-γ-diethylaminopropylamino-6-methylpyrimidine; it was a colourless oil, b. p. 194—195°/0·5 mm. (Found: C, 66·0; H, 7·7. $C_{19}H_{30}O_2N_4$ requires C, 66·3; H, 8·1%) (5932). The *dipicrate* crystallised from 2-ethoxyethanol in thick yellow laminæ, m. p. 155—156° (Found: C, 46·7; H, 4·3; N, 17·8. $C_{19}H_{30}O_2N_4$,2$C_6H_3O_7N_3$ requires C, 46·4; H, 4·2; N, 17·5%).

4-γ-*Diethylaminopropylamino*-6-p-*chlorophenylthio*-2-*methylpyrimidine* (III; R = Cl, R′ = [CH$_2$]$_3$·NEt$_2$, X = S).—Sodium (1·4 g.) was dissolved in alcohol (100 c.c.), *p*-chlorothiophenol (8·2 g.) and 4-chloro-6-γ-diethylaminopropylamino-2-methylpyrimidine (forthcoming publication) (15 g.) were added, and the solution was boiled under reflux for 6 hours. Water (200 c.c.) was added, and the solution made strongly alkaline with sodium hydroxide and extracted with benzene. Evaporation of the dried benzene extract and distillation of the residue gave the *pyrimidine*, b. p. 202—210°/2 mm., which set to a crystalline mass (yield, 13·6 g.) and then separated from light petroleum (b. p. 80—100°) in small colourless cubes, m. p. 75° (Found: C, 59·8; H, 7·2; S, 8·4. $C_{18}H_{25}N_4ClS$ requires C, 59·3; H, 6·8; S, 8·8%) (5342).

4-δ-*Diethylamino-α-methylbutylamino*-6-p-*chlorophenylthio*-2-*methylpyrimidine* (III; R = Cl, R′ = CHMe·[CH$_2$]$_3$·NEt$_2$, X = S).—*p*-Chlorothiophenol (14·5 g.) and 4-chloro-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (forthcoming publication) (14·2 g.) were fused at 120° for 3 hours and the mixture worked up as described above. The *product* was obtained as a pale yellow oil, b. p. 220—222°/0·1 mm. (yield, 13·3 g.) (Found: C, 60·8; H, 7·2; Cl, 9·5; S, 8·3. $C_{20}H_{29}N_4ClS$ requires C, 61·2; H, 7·4; Cl, 9·05; S, 8·15%) (5727).

Condensation of 2-*Chloro*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (12·1 g.) and *p*-chloroaniline (12·5 g.) were heated at 150—160° for 6 hours. The resulting melt was dissolved in warm dilute hydrochloric acid, and the solution made strongly alkaline with sodium hydroxide and extracted with chloroform. The chloroform solution was dried and evaporated, leaving an oil which was distilled under reduced pressure, the fraction b. p. 204—208°/0·2 mm. being collected. Its identity with 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine was proved by conversion into the dipicrate, m. p. 218—219°, either alone or mixed with authentic dipicrate (Part I, *loc. cit.*) (Found: C, 43·7; H, 4·1. Calc. for $C_{17}H_{24}N_6Cl$,2$C_6H_3O_7N_3$: C, 44·0; H, 3·8%), and the dihydrochloride, m. p. and mixed m. p. 267°.

2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (4·5 g.) and saturated alcoholic ammonia (20 c.c.) were heated in a sealed tube at 175—185° for 6 hours. The mixture was evaporated to dryness, and the residue stirred with water, made alkaline with sodium hydroxide, and extracted with ether. Evaporation of the dried ethereal extract and distillation of the residue gave a product, b. p. 148—152°/0·15 mm., which then crystallised from light petroleum (b. p. 60—80°). It had m. p. 70—72° either alone or mixed with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine (Part III, *loc. cit.*), and gave a dipicrate, m. p. 216—217°, undepressed in admixture with that previously described.

Condensation of 2-*Chloro*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-γ-diethylaminopropylamino-6-methylpyrimidine (5·12 g.) and *p*-chloroaniline (2·55 g.) were brought into reaction in a mixture of water (25 c.c.) and acetone (10 c.c.) (boiling) containing 10N-hydrochloric acid (2·2 c.c.) for 2 hours to give, after basification with sodium hydroxide and extraction with chloroform 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine (I; R = Cl, R′ = [CH$_2$]$_3$·NEt$_2$, X = NH), b. p. 210—216°/0·15 mm., identified as its dipicrate, m. p. 225—226°, which was identical with an authentic sample (Part I, *loc. cit.*). When the above reaction was attempted using only 0·2 c.c. of 10N-hydrochloric acid no appreciable condensation occurred during 2 hours' refluxing.

Condensation of 2-*Chloro*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine with* p-*Chloroaniline*.—2-Chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (5·68 g.) and *p*-chloroaniline (2·55 g.) were brought into reaction in boiling water (25 c.c.) containing 10N-hydrochloric acid (2·2 c.c.) during 2 hours. The cooled solution was made alkaline with sodium hydroxide and the precipitated oil separated. This was dissolved in 5% acetic acid, and the extract clarified with carbon, filtered, and made alkaline with sodium hydroxide. The liberated base was then extracted with chloroform, and the solution dried and evaporated. Distillation of the residual oil gave a product, b. p. 204—206°/0·15 mm., which afforded a dipicrate, m. p. 170—172°, identical with that of 2-*p*-chloroanilino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (Part I, *loc. cit.*) (Found: C, 46·0; H, 4·4; N, 18·8. Calc. for $C_{20}H_{29}N_6Cl$,2$C_6H_3O_7N_3$: C, 46·1; H, 4·3; N, 18·5%).

2-Amino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine.—2-Chloro-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (5 g.) and saturated alcoholic ammonia (20 c.c.) were heated in a sealed tube for 6 hours at 180—190°. After evaporation to dryness, the contents of the tube were dissolved in water and made alkaline with sodium hydroxide. The product, isolated by extraction with chloroform, was purified by vacuum distillation, the fraction b. p. 148—150°/0·14 mm. being collected (yield, 4·1 g.). With picric acid in methanol it gave a *dipicrate* which crystallised from 2-ethoxyethanol–alcohol in yellow laminæ, m. p. 170—171°, not depressed in admixture with that prepared from the authentic compound (Part III, *loc. cit.*) (Found: C, 43·1; H, 4·5; N, 21·9. $C_{14}H_{27}N_3,2C_6H_3O_7N_3$ requires C, 43·2; H, 4·6; N, 21·3%).

2-p-*Chloroanilino-4-phenoxy-6-methylpyrimidine.*—Potassium hydroxide (11·2 g.) was treated with 4 drops of water and fused. Phenol (56·4 g.) was added and the mixture heated to 120—130°. 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (Part I) (25·4 g.) was added gradually during 20 minutes with stirring. After being stirred at 120—130° for a further ½ hour, the mixture was cooled and treated with sodium hydroxide solution, and the product extracted with ether. After being washed with alkali and then with water, the ether solution was dried and evaporated and the residue crystallised from alcohol, giving the *pyrimidine* as colourless needles, m. p. 126° (Found: N, 13·5; Cl, 11·6. $C_{17}H_{14}ON_3Cl$ requires N, 13·5; Cl, 11·4%).

Condensation of 2-p-*Chloroanilino-4-phenoxy-6-methylpyrimidine with β-Diethylaminoethylamine.*—The above phenoxy-compound (15·5 g.), phenol (45 g.), and β-diethylaminoethylamine (7·25 g.) were stirred and heated at 120—130° for 8 hours. After cooling, water and sodium hydroxide were added and the insoluble material was taken into chloroform. The chloroform solution was shaken several times with 5% acetic acid (evaporation of the dried chloroform solution gave unchanged 2-*p*-chloroanilino-4-phenoxy-6-methylpyrimidine, 10·6 g.), and the combined acetic acid extracts were made alkaline with sodium hydroxide and extracted with chloroform. The chloroform was then extracted thoroughly with 2N-hydrochloric acid and the extract evaporated to dryness under reduced pressure. Crystallisation of the dried residue from alcohol gave 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. and mixed m. p. 266—267° (yield, 28·6%). Separate experiments showed that β-diethylaminoethylamine mono- and di-hydrochlorides could be used in place of β-diethylaminoethylamine in the above condensation.

Condensation of 2-p-*Chloroanilino-4-phenoxy-6-methylpyrimidine and γ-Diethylaminopropylamine.*—2-*p*-Chloroanilino-4-phenoxy-6-methylpyrimidine (15·5 g.) and γ-diethylaminopropylamine (8·12 g.) were brought into reaction in phenol (45 g.), and the reaction mixture treated as in the previous experiment, giving unchanged 2-*p*-chloroanilino-4-phenoxy-6-methylpyrimidine (9·7 g.) and 2-*p*-chloroanilino-4-γ-diethylaminopropylamino-6-methylpyrimidine dihydrochloride (yield, 16·3%), m. p. (after one crystallisation) and mixed m. p. 246—248°.

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[*Received, September 10th*, 1946.]

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153. *Kinetics of Nitrous Gas Absorption in Aqueous Nitric Acid.*

By K. G. DENBIGH and A. J. PRINCE.

Measurements have been made in a falling-film tower on the rate of reaction of nitrous gas with aqueous nitric acid of concentration 10—60%. Both gas and acid were circulated in closed systems, and the rate of absorption or evolution of nitrogen dioxide was determined by measurement of the rate of change of colour intensity of the circulating gas.

It was found that the absorption or evolution rate per unit area of interface could be expressed by the equation

$$V = k_a \{[N_2O_4] - C[N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}\}$$

Here $[N_2O_4]$ and $[NO]$ refer to the concentrations in the gaseous phase and C is a constant which can be calculated from the known equilibrium constant of the reaction. The equation expresses fairly closely the measured velocity over a wide range of gas compositions and in both directions of the reaction, which is reversible.

The overall reaction in question is expressed by the equation $3NO_2 + H_2O \rightleftharpoons 2HNO_3 + NO$. The theoretical derivation of the above expression is based on the assumption that the actual rate-limiting step is the elementary reaction $N_2O_4 + H_2O \rightleftharpoons HNO_3 + HNO_2$. An alternative treatment, based on the assumption that the diffusional processes are rate-limiting, has given less satisfactory results.

Increase of acid concentration greatly increases the value of the constant C. It follows that the rate of absorption of nitrogen dioxide is much reduced at high acid concentrations (*e.g.*, over 40%), owing to the intrinsic reversibility of the reaction.

Increase in temperature causes a considerable decrease in the rate of absorption of dioxide. This is partly due to changes in the values of k_a and C, but is mainly a result of a shift in the equilibrium between NO_2 and N_2O_4. It appears that it is the latter which is the more reactive species in the total dioxide. The present results do not allow of any final conclusions with regard to a possible effect of gas-flow rate on the coefficient k_a. The application of the results to the design of nitric acid plants will be discussed elsewhere.

THE reaction of nitrogen dioxide with water proceeds mainly according to the following stoicheiometric relation:

$$3NO_2 \text{ (or } 1\tfrac{1}{2}\ N_2O_4) + H_2O \rightleftharpoons 2HNO_3 + NO \quad . \ . \ . \ . \ . \ . \ (A)$$

A certain amount of nitrous acid is also formed, but the quantity is generally quite small under conditions of efficient agitation of the liquid phase, as in a falling-film tower. The kinetics of the process may be expected to be somewhat complex, owing to the high degree of reversibility of the reaction (A) and also to the large number of molecular species which can take part in the various elementary reactions. These are NO_2, N_2O_4, NO, N_2O_3, H_2O, HNO_3, and HNO_2. Moreover, the observed absorption rate might be controlled either by chemical reaction or by diffusional processes. Under plant conditions, additional complications arise from the variations in conditions from one section of plant to another and also from the occurrence of the oxidation reaction

$$2NO + O_2 \longrightarrow 2NO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

The overall performance of a nitrous gas absorption plant is determined by the rate of both the reactions (A) and (B). Detailed kinetic information is available, however, only for the latter reaction, which has been studied extensively by Bodenstein and others. The only exact research on the rate of the absorption reaction is that of Chambers and Sherwood (*Ind. Eng. Chem.*, 1937, **29**, 1415). These workers investigated the effect of acid concentration and gas-flow rate at an almost constant gas composition. It was concluded that the rate of absorption was dependent on the speed of diffusion through a film of stagnant gas and mist at the interface.

The experimental work described below was carried out in 1937, before the publication of Chambers and Sherwood's work. The object was primarily to determine the effect on the absorption rate of (*a*) the composition of the gaseous phase, (*b*) the concentration of the acid, and (*c*) the temperature. These are the variables which are probably the most important in plant practice. The possible effects of gas and acid flow rates were given only a cursory examination and the values of these variables were generally kept at approximately the values which are realised in an absorption plant operating at atmospheric pressure.

The work has thus given values for the absorption rate under various conditions which are of technical interest and has been made a basis of the successful design of certain war-time nitric acid plants, as will be shown in a later paper. The results have also given some indications of the possible mechanism of the absorption process.

Experimental.

(a) *General Description of Method.*—The experimental method consisted in the circulation of a nitrous gas–nitrogen mixture round a closed system which contained a small falling-film tower. The concentration of nitrogen dioxide in the gaseous phase was determined by measurement of the colour intensity of the circulating gas by use of a photoelectric cell. Measurements of the colour intensity, and also of the total pressure of the circulating gas, were made at 30-second intervals during the course of the absorption and from these data, and the known equilibrium constants, the concentrations of each of the species NO_2, N_2O_4, NO, and N_2O_3 could be evaluated. The velocities were then obtained by taking tangents to the concentration curves.

The advantage of this method was that, since the gas composition changed during the course of each run, data were thus obtained on the effect on absorption rate of a much larger range of gas compositions than could otherwise have been examined. The acid was also circulated. Its concentration did not alter greatly during the course of each run.

The main items of the apparatus (Fig. 1) were as follows: absorption tower, *a*; electromagnetic pump, *b*, for acid circulation; blower, *c*, for gas circulation; gas reservoir, *d*; manometer, *e*; colour-chamber, *f*; lamp, *g*; photocell, *h*; gas flow-meter, *j*; acid flow-meter, *k*; acid reservoir, *l*. The NO_2 and NO preparation apparatus, the vacuum system, and the potentiometer circuit, used in conjunction with the photocell, are not shown in the diagram. In the manometer (*e*), the mercury was protected from attack by a ¼ in. layer of α-bromonaphthalene.

(b) *Details of Gas and Acid Circulation.*—The falling-film tower was of 1¼ in. internal diameter and about 5 in. long. The absorption surface, computed from the dimensions, included the surface of the acid in the weir and in the foot of the tower.

The volume of the gas circulation system was 6·72 l., of which 0·51 l. was outside the thermostat. The gas-flow rate was generally of the order of 10—13 l./min. and was sufficient to give turbulent (or at least eddying) conditions in the absorption tower, as indicated in preliminary experiments with smoke.

The blower *c* (designed by Mr. R. A. Smith) was constructed of stainless steel and had a centrifrugal liquid seal surrounding the driving shaft, in order to prevent air leakage into the apparatus when the pressure was below atmospheric. This seal consisted of a disc *m* which was mounted on the shaft and rotated above a bath of liquid housed over the impellor casing. Round the periphery of the disc there was a wide flange which dipped into the liquid; the high speed of rotation (4000 r.p.m.) and the friction of the flange caused the liquid in the seal to be raised into a vertical ring; this sealed the periphery of the disc against the housing and very effectively prevented any leakage even at pressures as low as half an atmosphere.

Much difficulty was experienced in finding a suitable liquid for this seal, on account of the tendency of the nitrous gas to be transmitted through the liquid to the external atmosphere, by solution. Mercury was finally chosen, although it suffered from the disadvantage of reacting with the nitrous gas in the blower until the surface of the mercury had become covered with corrosion product.

(c) *Measurement of the Nitrogen Dioxide Concentration.*—Of the gases present in the apparatus only the dioxide had appreciable absorption for light of wave-lengths within the range of sensitivity of the photocell. The determination of the colour intensity thus gave an instantaneous measure of the concentration of this oxide.

The current from the photocell, which was of the rectifier type, was passed through an external resistance, and the potential difference across this resistance was measured by use of a potentiometer. The illumination was by means of a 24-watt motor-car lamp operating on two 12-volt accumulators in parallel. The discharge of the accumulators caused a slow and steady fall in the zero reading of the photocell and it was necessary to allow for this in each absorption run.

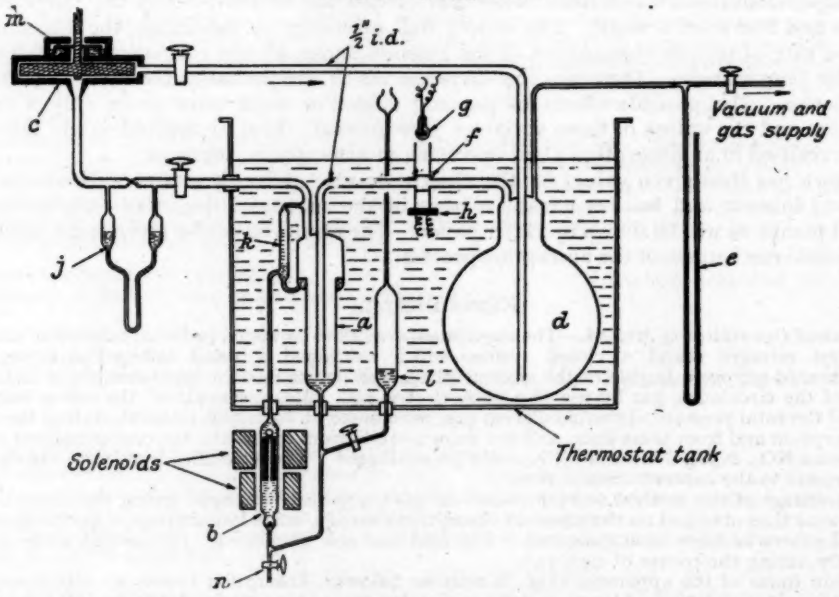
The photoelectric equipment was calibrated against measured pressures of nitrogen dioxide in the apparatus before each run, and the function $\log E/E_0$ was plotted against p_{NO_2}. Here E_0 is the P.D. at zero dioxide pressure and E is the potential difference at partial pressure p_{NO_2}. This calibration was found to vary very little from day to day and was also found to be unaffected by the vibration of the blower.

(d) *Details of Experimental Procedure.*—Nitrogen dioxide, prepared by heating lead nitrate, was dried, liquefied, and fractionated to constant vapour pressure.

In carrying out an absorption experiment the blower, whilst running, was first blown through with nitrogen. The rest of the apparatus was evacuated, and dioxide was then admitted in small batches, and at each batch the photocell reading was calibrated against the measured pressure. Finally, a

FIG. 1.

Diagram of Apparatus.



measured quantity of nitrogen was admitted as a diluent, and the gas was put into circulation by means of the blower. Then, when conditions were steady, the acid was introduced from the reservoir, *l*, and the electro-magnetic pump was set into operation. Complete wetting of the tower was attained within 5—10 seconds. An electrical device was caused to sound a bell at 30-second intervals throughout the run, and at these moments simultaneous readings were taken on the manometer and potentiometer. The readings were continued for 10—20 minutes, by which time they had become constant, the acid and gas having come to equilibrium. Finally, the acid was released from the apparatus through tap *n* (and was subsequently analysed for HNO_3 and HNO_2) and the nitrous gas was purged out of the apparatus with air, in order to obtain a check on the zero of the photoelectric equipment.

In a few experiments the reaction was carried out in the reverse direction, by using an initial gas consisting of nitric oxide in nitrogen. In these runs it was the rate of *evolution* of nitrogen peroxide which was measured.

(e) *Treatment of Experimental Results.*—The photocell readings were used to calculate directly the instantaneous values of the NO_2 concentration in the circulating gas. Since the NO_2–N_2O_4 equilibrium is set up extremely rapidly (Selle, *Z. physikal. Chem.*, 1923, **104**, 1) the corresponding N_2O_4 concentrations could be calculated by use of the Bodenstein equilibrium constant (*ibid.*, 1922, **100**, 75). The total concentration, $[NO_2] + 2[N_2O_4]$, was thus known throughout the run. (A small correction for the presence of very low concentrations of N_2O_3 was applied.) Then, knowing the volume of the apparatus and the area of absorbing acid surface, it was possible to obtain the rate of absorption (or evolution) of total dioxide per unit surface, by taking chords between the successive measured points on the concentration curve. The method was thus only dependent on the accuracy of the photocell readings ($\pm$ 0·001 ats. partial pressure of NO_2) and on the calculation of the equilibrium concentration of N_2O_4.

The other molecular species present in the gaseous phase at any moment were N_2, N_2O_3, NO, and HNO_3, and H_2O vapour. (The vapour pressure of HNO_3 was neglected as it is very small; Abel, *Monatsh.*, 1929, **54**, 855; *Z. physikal. Chem.*, 1928, **136**, 430.) Approximate values for the H_2O and HNO_3 partial pressures were estimated at each moment of the run from the data of subsidiary experiments in which the rate of vaporisation of acid of various concentrations was measured in the falling-film tower. The value of the nitrogen partial pressure was known, being equal to that which was introduced into the apparatus at the beginning of the experiment. The sum, S, of the NO and N_2O_3 concentrations was then obtained by difference, and the individual values of these concentrations were then calculated by solving the two equations, $[NO] + [N_2O_3] = S$ and $[N_2O_3] = K'[NO][NO_2]$, where K' is Abel and Proisl's equilibrium constant (*Z. Electrochem.*, 1929, **35**, 712).

The main sources of inaccuracies in the results were as follows. (1) The gas flow-rate was rather variable and tended to decrease during the course of a run. (2) There was an uncertainty in the temperature amounting to $\pm 2°$, owing to the blower's being outside the thermostat tank. (However, the absorption rate was not found to be very dependent on temperature.) (3) The area of absorbing surface in the falling-film tower was indefinite to the extent of 2—3%. (4) There was an uncertainty of $\pm$ 1 second in the taking of the potentiometer and pressure readings at the desired moment. (5) The mercury in the blower seal reacted with nitrogen dioxide and at an appreciable rate, at least until the mercury had become covered with corrosion product. (The course of the reaction was tested by experiment, as there is some controversy in the literature, and it was found to be $2NO_2 + Hg = HgNO_3 + NO$.) In each run the acid was not admitted to the absorption tower until the reaction with the mercury had become relatively slow.

It is evident that there were appreciable inaccuracies, probably not exceeding 10%, due to the difficulties of the technique. A summary of the results obtained in the most satisfactory runs is given in Tables I, II, and III. In these tables col. 2 gives the time in minutes from the moment the acid

TABLE I.

Rate of dioxide absorption at 25°, (kg.-moles NO_2/m^2. sec.) $\times 10^6$.

(I.A. and F.A. are initial and final acids, respectively, in $\%HNO_3$ and $\%HNO_3$; G.R. = gas rate, l./min.; A.R. = acid rate, c.c./min.)

Details.	Time, mins.	Concns., g.-moles/l. $\times 10^3$. NO_2.	NO.	Abs. rate.	Acid concn., %.	$k_f \times 10^3$, Eq. (3).	$k_s \times 10^3$, Eq. (4).	$k_s \times 10^3$, Eq. (7).
	0·0	4·2	3·7	—	9·5	—	—	—
I.A. 9·5%, 0·0%	0·5	3·6	3·5	36	10·1	3·6	1·7	1·7
F.A. 11·8%, 0·85%	1·0	3·0	3·4	28	10·6	3·8	1·9	1·9
G.R. 12	1·5	2·6	3·3	22	10·9	3·8	1·9	1·9
A.R. 310	3·0	1·6	3·2	10	11·4	3·4	2·3	2·3
	4·0	1·2	3·3	5	11·6	2·5	2·0	2·0
	0·0	7·6	4·9	—	9·5	—	—	—
I.A. 9·5%, 0·0%	0·5	6·0	5·2	100	12·0	4·3	1·7	1·7
F.A. 16·5%, 1·3%	1·0	5·1	5·4	65	13·0	3·7	1·6	1·6
G.R. 10	2·0	3·9	5·8	32	14·4	2·9	1·3	1·3
A.R. 310	3·0	3·1	6·3	20	15·1	2·6	1·3	1·3
	4·0	2·5	6·9	13	15·5	2·4	1·3	1·3
	6·0	1·6	7·8	6	16·0	2·1	1·4	1·4
	0·0	6·9	4·0	—	9·3	—	—	—
I.A. 9·3%, 0·0%	1·0	4·5	5·0	70	12·2	4·9	2·1	2·1
F.A. 15·3%, 1·3%	1·5	3·7	5·3	47	13·1	4·6	2·1	2·1
G.R. 0—2·8 mins., 10; from 2·8	2·0	3·05	5·7	33	13·7	4·4	2·1	2·1
mins. on, 8	2·5	2·5	6·1	22	14·1	4·1	2·1	2·1
A.R. 680	3·0	2·1	6·3	15	14·5	3·7	2·0	2·0
	4·0	1·55	6·8	8	14·9	2·9	2·0	2·0
	0·0	6·7	2·5	—	14·7	—	—	—
I.A. 14·7%, 1·2%	0·5	5·4	4·0	90	16·4	4·7	1·8	1·8
F.A. 20·4%, 1·1%	1·0	4·6	4·6	58	17·4	3·9	1·7	1·7
G.R. 10	1·5	3·8	5·3	42	18·2	3·9	1·7	1·7
A.R. 0—3 mins., 650; from 3	2·0	3·4	5·8	31	18·6	3·4	1·6	1·6
mins. on, 790	3·0	2·5	6·7	19	19·3	3·5	1·8	1·8
	4·0	1·8	7·5	11	19·7	3·2	2·0	2·1
	0·0	5·5	1·4	—	44·3	—	—	—
I.A. 44·3%, 0·0%	1·5	3·9	2·9	27	44·7	—	—	1·3
F.A. 45·1%, *ca.* 0·6%	2·0	3·4	3·2	22	44·8	—	—	1·4
G.R. 5	3·0	2·8	3·7	13	44·9	—	—	1·4
A.R. 310	5·0	2·05	4·4	5	45·0	—	—	1·5
	12·0	1·4	5·0	0	45·1	—	—	—
	18·0	1·4	5·0	0	45·1	—	—	—
	0·0	7·9	7·1	—	44·3	—	—	—
I.A. 44·3%, 0·0%	2·0	4·9	10·2	47	45·6	—	—	1·5
F.A. 46·4%, *ca.* 1·2%	3·0	4·0	11·2	26	45·9	—	—	1·4
G.R. 9	4·0	3·4	11·7	16	46·1	—	—	1·4
A.R. 310	16·0	2·2	13·1	0	46·4	—	—	—

TABLE II.

Dioxide absorption at 40°. (Units, etc., as in Table I.)

Details.	Time, mins.	Concns., NO_2.	Concns., NO.	Abs. rate.	Acid concn., %.	$k_3 \times 10^3$, Eq. (3).	$k_4 \times 10^2$, Eq. (4).	$k_4 \times 10^2$, Eq. (7).
	0·0	4·5	1·8	—	9·6	—	—	—
I.A. 9·6%, 0·0%	0·5	3·9	1·6	17	9·8	2·7	2·0	2·0
F.A. 11·1%, 0·3%	1·0	3·5	1·6	13	10·0	2·4	1·9	1·9
G.R. —	1·5	3·1	1·6	10	10·2	2·1	1·9	1·9
A.R. 310	2·0	2·7	1·6	9	10·4	2·4	2·1	2·1
	0·0	6·5	7·0	—	9·5	—	—	—
I.A. 9·5%, 0·0%	0·5	5·45	6·8	35	9·9	3·4	2·1	2·1
F.A. 11·5%, 0·8%	1·0	4·65	6·5	27	10·2	3·3	2·2	2·2
G.R. 11	2·0	3·35	6·6	14	10·6	2·7	2·2	2·2
A.R. 0—1·75 mins., 310;	2·5	2·95	6·8	11	10·8	2·6	2·2	2·2
from 1·75 mins. on, 220	3·0	2·65	6·9	9	10·9	2·4	2·2	2·2
	4·0	2·1	7·1	5	11·1	1·8	2·0	2·0
	0·0	8·7	8·2	—	9·5	—	—	—
I.A. 9·5%, 0·0%	0·5	7·3	8·0	57	10·2	3·6	1·9	1·9
F.A. 13·2%, 0·9%	1·0	6·1	8·0	44	10·9	3·6	2·1	2·1
G.R. 11	1·5	5·1	8·3	33	11·4	3·5	2·3	2·3
A.R. 310	2·0	4·2	8·6	25	11·7	3·6	2·5	2·5
	3·0	2·9	9·4	14	12·3	3·3	2·9	2·9
	4·0	2·15	10·1	8	12·5	2·9	3·1	3·2
	0·0	6·6	5·3	—	30·1	—	—	—
I.A. 30·1%, 0·0%	0·5	5·5	5·0	42	30·4	4·0	2·5	2·6
F.A. 31·9%, 0·5%	1·0	4·6	5·3	30	30·7	3·8	2·5	2·8
G.R. 12	1·5	3·9	5·6	23	31·0	3·6	2·7	3·0
A.R. 310	2·0	3·3	5·8	18	31·2	3·5	2·9	3·4
	3·0	2·4	6·2	10	31·4	3·1	3·1	4·0
	0·0	9·9	7·0	—	30·1	—	—	—
I.A. 30·1%, 0·0%	0·5	8·2	7·6	75	30·8	4·0	2·0	2·1
F.A. 33·6%, 0·7%	1·0	6·9	8·1	52	31·3	3·6	2·0	2·1
G.R. 11	1·5	5·9	8·5	42	31·7	3·6	2·1	2·3
A.R. 310	2·0	5·2	8·9	33	32·0	3·4	2·2	2·4
	3·0	3·9	9·5	20	32·5	3·1	2·3	2·9
	4·0	3·0	10·0	12	32·9	2·7	2·4	3·4
	0·0	9·6	6·7	—	37·1	—	—	—
I.A. 37·1%, 0·0%	0·5	7·6	7·7	75	37·5	—	—	2·6
F.A. 39·0%, 0·7%	1·0	6·3	8·2	48	37·9	—	—	2·6
G.R. 13	1·5	5·4	8·6	34	38·1	—	—	2·6
A.R. 0—2¼ mins., 310;	2·0	4·6	8·9	25	38·3	—	—	2·8
from 2¼ min. on, 270	2·5	4·1	9·3	18	38·4	—	—	2·7
	3·0	3·7	9·5	13	38·5	—	—	2·7
	0·0	10·5	5·1	—	44·3	—	—	—
I.A. 44·3%, 0·0%	1·0	7·5	6·8	41	45·5	—	—	1·9
F.A. 46·6%, 0·7%	1·5	6·6	7·1	29	45·8	—	—	1·9
G.R. 10	2·0	6·0	7·4	20	46·1	—	—	1·8
A.R. 0—1½ mins., 330; from	3·0	5·3	7·8	10	46·3	—	—	1·4
1½ mins. on, 240								
	0·0	6·4	4·5	—	43·9	—	—	—
I.A. 43·9%, 0·0%	0·5	5·7	4·4	25	44·0	—	—	2·0
F.A. 44·3%, *ca.* 0·5%	1·0	5·0	4·6	19	44·1	—	—	2·1
G.R. 8	1·5	4·55	4·7	15	44·2	—	—	2·2
A.R. 310	2·0	4·15	4·8	11	44·2	—	—	2·2
	0·0	7·8	4·9	—	44·3	—	—	—
I.A. 44·3%, 0·0%	0·5	6·9	5·0	25	44·6	—	—	1·3
F.A. 45·7%, 0·6%	1·0	6·4	5·1	20	44·8	—	—	1·2
G.R. 3	1·5	5·9	5·2	16	45·0	—	—	1·2
A.R. 310	2·0	5·5	5·3	13	45·1	—	—	1·2
	3·0	4·9	5·6	8	45·3	—	—	1·1
	0·0	8·6	7·5	—	44·4	—	—	—
I.A. 44·4%, 0·0%	0·5	7·6	7·7	34	44·6	—	—	1·4
F.A. 45·5%, 0·8%	2·0	6·3	8·3	18	45·1	—	—	1·4
G.R. 4	3·0	5·6	8·5	12	45·2	—	—	1·3
A.R. 220	4·0	5·2	8·7	8	45·3	—	—	1·2
	0·0	12·4	5·0	—	59·2	—	—	—
I.A. 59·2%, 0·0%	0·5	11·5	5·3	45	59·2	—	—	2·1
F.A. 59·0%, 1·1%	1·0	10·9	5·4	25	59·1	—	—	1·7
G.R. 10	1·5	10·5	5·5	15	59·0	—	—	1·5
A.R. 310	2·0	10·3	5·5	10	59·0	—	—	1·2

TABLE III.

Dioxide evolution at 25° and 40°. (Units, etc., as in Table I.)

Details.	Time, mins.	Concns., NO_2.	Concns., NO.	Evoln. rate.	Acid concn., %.	$k_2 \times 10^2$, Eq. (7).
40°.	0·0	0·4	10·8	(8)	43·9	—
I.A. 43·9%, 0·0%	1·0	1·1	9·5	6	43·4	2
F.A. 42·1%, *ca.* 0·6%	2·0	1·6	8·8	4	42·8	2
G.R. 9	12·0	2·6	7·6	0	42·1	—
A.R. 310	18·0	2·6	7·8	0	42·1	—
40°.	0·0	0·0	19·7	(45)	52·1	—
I.A. 52·1%, 0·0%	1·0	3·7	16·7	35	50·6	3·0
F.A. 49·2%, 0·9%	2·0	5·1	15·1	20	49·9	3·9
G.R. 14	7·5	6·1	14·0	0	49·2	—
A.R. 310	10·5	6·1	14·0	0	49·2	—
40°.	0·0	0·0	21·9	(70)	59·2	—
I.A. 59·2%, 0·0%	0·5	3·4	17·4	62	57·5	1·7
F.A. 53·6%, 0·6%	1·0	5·0	15·7	51	56·3	1·8
G.R. 16	1·5	6·3	14·4	39	55·3	2·0
A.R. 310	2·0	7·0	13·7	27	54·6	2·3
	12·0	8·0	13·9	0	53·6	—
40°.	0·0	0·3	15·6	(45)	59·2	—
I.A. 59·2%, 0·0%	0·5	2·2	13·7	42	58·2	1·3
F.A. 54·6%, 1·1%	1·0	3·6	12·4	40	57·3	1·4
G.R. 11	1·5	4·7	11·4	35	56·5	1·4
A.R. 310	2·0	5·7	10·6	22	55·8	1·3
25°.	0·0	0·0	10·9	—	44·3	—
I.A. 44·3%, 0·0%	0·5	0·1	10·7	1·5	44·1	—
F.A. 42·5%, *ca.* 0·8%	1·0	0·2	10·2	2	44·0	—
G.R. 10	2·0	0·4	9·6	3	43·8	—
A.R. 310	4·0	0·8	8·8	2	43·3	—
	12·0	1·25	8·1	0	42·5	—
25°.	0·0	0·0	20·4	(85)	59·0	—
I.A. 59·0%, 0·0%	0·5	2·2	17·5	46	57·4	1·7
F.A. 55·3%, 1·6%	1·0	3·0	15·9	32	56·4	1·7
G.R. *ca.* 12	1·5	3·4	15·1	20	56·0	1·4
A.R. 310	2·0	3·7	14·5	13	55·7	1·3
	8·5	3·9	13·6	0	55·3	—

started to flow down the absorption tower, and cols. 3 and 4 give the corresponding concentrations of NO_2 and NO. The concentrations of N_2O_4 and N_2O_3 are not shown in the tables, but are readily calculable by use of the equilibrium constants. The estimated partial pressures of H_2O and HNO_3 vapour are also not shown but were very small. The partial pressure of diluent nitrogen was that necessary to make the total pressure up to 1 atm. at the commencement of each run.

The gaseous concentrations are expressed as g.-moles/l., which is equivalent to kg.-moles/m.^{3}. The absorption or evolution rate is expressed as kg.-moles/m^2. sec., a unit convenient for application of the results in plant practice.

Details of the initial and final acid concentrations, etc., are given in col. 1, together with interpolated figures in col. 6. The figures quoted for HNO_3 include the dissolved nitrous gas expressed as HNO_3, as determined by titration with permanganate.

In order to economise space, the tables do not include the results obtained at all the time intervals in each run; in particular, the data obtained when the absorption rate had become too low to be accurately measurable have been omitted. However, in those runs in which the gas composition appeared to reach a definite constancy, the limiting values have been included for use in calculating the equilibrium constant.

Qualitative Results.—Certain qualitative results and observations were as follows.

(*a*) The rate of dioxide absorption was found to be greater the higher its concentration and the lower the nitric oxide concentration. Similarly, in those runs in which the reaction was carried out in the reverse direction, the rate of nitric oxide absorption was greater the higher its concentration and the lower the dioxide concentration.

(*b*) At the same concentration of total dioxide and of nitric oxide the rate of absorption of dioxide was greater at 25° than at 40°.

(*c*) Increase of acid concentration caused a decrease in the rate of absorption of dioxide. Conversely, an increase of acid concentration caused an increase in the rate of absorption of NO, in those runs in which the reaction rate was measured in the reverse direction. The rate of reaction of NO with dilute acids was very low.

(*d*) An initially colourless and nitrous-free acid was generally used in the experiments, but after circulation in the tower a green colour always developed. This coloration came to a maximum within 1—2 minutes after first introduction of the acid and then remained apparently constant. It was the more marked the more concentrated the acid. At the end of each run, a titration with permanganate usually gave 0·5—1·5% of nitrous acid and dissolved gas, both reckoned as HNO_3.

(*e*) The tangent to the curve of the NO concentration could be used to calculate an approximate figure for its rate of evolution. This was generally less than one-third of the rate of dioxide absorption, and this was no doubt due to the formation of nitrous acid and to nitric oxide remaining in solution after the occurrence of the reaction. It appeared that the liquid phase became saturated with nitrous acid and dissolved gas during the first 1 or 2 minutes of each run, and thereafter the nitric oxide was evolved. In some of the runs colourless gas could be seen to be bubbling out of solution in the acid in the pump.

(*f*) No formation of visible mist was observed, in contrast to Chambers and Sherwood's observations. There was some condensation of acid in the gas blower, but none in the reservoir, *d*.

Discussion.

Treatment of Equilibrium Data.—The equilibrium constant of reaction (A) is given by

$$K = \frac{p_{NO} \cdot p^2_{HNO_2}}{p^3_{NO_2} \cdot p_{H_2O}} = K_1 K_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $K_1 = p_{NO}/p^3_{NO_2}$ and $K_2 = p^2_{HNO_2}/p_{H_2O}$ (pressures in atms.); K_1 and K_2 are not true constants but are convenient factors into which to split K. In particular, K_1 will vary with change of acid concentration.

The equilibrium partial pressures of NO_2 and NO, as measured in those runs in which the gas composition became constant, are shown in Table IV, together with the corresponding calculated values of K_1. The data include results from runs carried out on both the forward and the reverse direction of the reaction as indicated by the letters F and R.

Table IV.

Equilibrium data.

		Equilibrium conditions.			
Run.	Temp.	HNO_2, %.	p_{NO_2}, atm.	p_{NO}, atm.	$\log_{10} K_1$.
R	25°	42·5	0·030	0·197	3·86
F	25	45·1	0·034	0·122	3·49
F	25	46·4	0·054	0·320	3·31
R	25	55·3	0·095	0·332	2·59
R	40	42·1	0·067	0·200	2·82
R	40	49·2	0·156	0·360	1·98
R	40	53·6	0·205	0·357	1·62

Values of K_1 have been determined experimentally by Abel, Schmid, and Stein (*Z. Electrochem.*, 1930, **36**, 692), Chambers and Sherwood (*J. Amer. Chem. Soc.*, 1937, **59**, 316), and Epshtein (*J. Gen. Chem. U.S.S.R.*, 1939, **9**, 792), using a variety of experimental methods. The values of $\log_{10} K_1$ obtained by these workers are shown in Fig. 2, together with the values from Table IV. It is evident that the values obtained in the present work are in very good agreement with those in the literature, and this gives support to the method of calculating the concentrations of nitrogen mon- and di-oxide in the gas-circulating system, as described previously. [Values of K_1 were also obtained by Burdick and Freed (*J. Amer. Chem. Soc.*, 1921, **43**, 518). Their values are different from the results of all the later workers and have not been included in Fig. 2. It has been suggested by Chambers and Sherwood that true equilibrium was not obtained in Burdick and Freed's experiments.]

The calculation of the equilibrium constant, K, of the reaction is dependent on a knowledge of the vapour pressure of nitric acid. The matter has been discussed by Forsythe and Giauque (*J. Amer. Chem. Soc.*, 1942, **64**, 48). For the present purpose a knowledge of K_1 is sufficient.

Diffusion Theory of Absorption Rate.—The experimental results for the absorption rate, as given in Tables I—III, have been expressed as the quantity of total dioxide absorbed per unit time *per unit area*. It has therefore been assumed that the rate is proportional to the area of the acid surface. Strong confirmation of this assumption is available from the results of Chambers and Sherwood. These workers used both a falling-film tower and a batch absorption vessel. The absorption rate, expressed per unit area of interface, was found to be about the same in the two types of apparatus, despite a large difference in the ratio of this area to the volumes of the bulk phases. The rate of reaction is thus determined by the area of the acid–gas interface. It seems likely that the reaction takes place either at the surface itself or in a region very close to it. This view is not inconsistent with the possibility of some reaction in the gaseous phase, resulting in mist formation, provided it takes place in the interfacial region, whose volume is proportional to the area of the absorbing surface.

Whilst this view of the process serves to reconcile various observations, it does not indicate the nature of the rate-limiting process. This might be the evaporation of water, the diffusion

of NO_2 and N_2O_4 into the interfacial region, the diffusion of NO out of the region, or finally the actual collisional process of the chemical reaction. In considering these different possibilities, it is necessary to bear in mind the reversibility of the reaction and the fact that any expression for the absorption rate must reduce to zero when the composition of the gaseous phase is that which is at equilibrium with the acid.

Chambers and Sherwood found that the rate of absorption was increased by raising the flow of gas. It was suggested therefore that the rate-limiting process was the diffusion of NO_2 and N_2O_4 up to the interface through a stagnant film of mist and inert gas. Their theoretical expression for the absorption rate, V, is then of the form

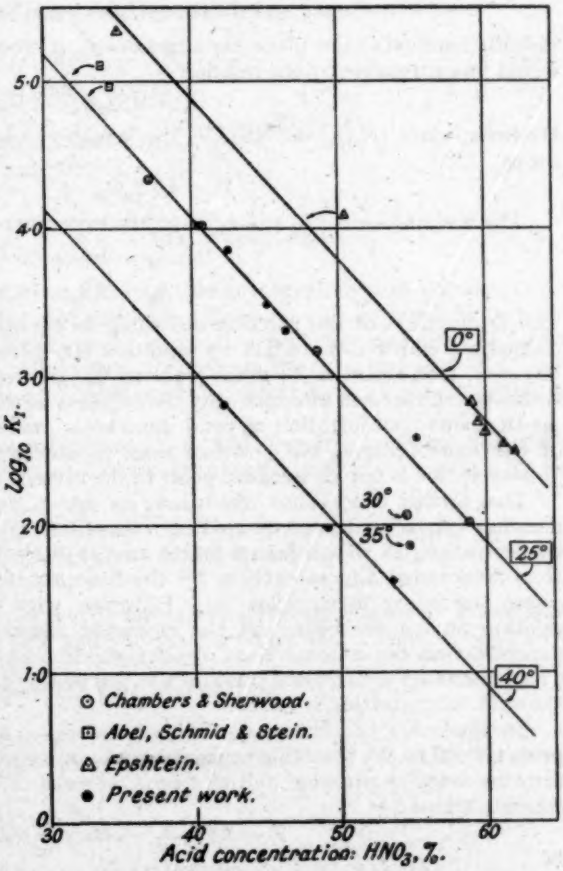
$$V = \frac{PD_{NO_2}}{RTp_B x}\left\{\frac{2D_{N_2O_4}}{D_{NO_2}} \cdot p_{N_2O_4} + p_{NO_2}\right\} \quad (2)$$

In this equation P is the total pressure, p_B the mean partial pressure of inert gas in the film, x the effective film thickness, and the D's and p's refer to the diffusion coefficients and partial pressures, respectively, of N_2O_4 and NO_2.

From the present point of view there are three objections to this expression. (1) The velocity, V, does not become zero when the concentrations of NO_2 and N_2O_4 are such that they are at equilibrium with the acid and with the NO. (2) No allowance is made for the very considerable effect of NO concentration on absorption rate. (3) Even with dilute acid, where the reverse reaction is negligible, the equation does not correctly express the effect of NO_2 and N_2O_4 concentration on the absorption rate.

With regard to the third point, the work of Chambers and Sherwood was carried out at an almost constant gas composition and they were therefore unable to show whether their theoretical expression was in agreement with experiment. Now the ratio $2D_{N_2O_4}/D_{NO_2}$ can be calculated from kinetic theory as 2·86, and the quantity outside the bracket in equation (2) can be taken as approximately constant in any one of the runs of the present work. The equation can therefore be rearranged as follows :

FIG. 2.



$\log_{10} K_1$ *plotted against* HNO_3 *concn.* (%).

$$\frac{V}{2{\cdot}86\,[N_2O_4] + [NO_2]} = k_g \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Values of k_g calculated from the present results are shown in col. 7 of Tables I and II. There is seen to be a pronounced fall in the value of k_g during the course of each experiment as the gas composition changes : k_g is thus not a true constant.

It seems, therefore, that the diffusion theory does not account very satisfactorily for the facts, especially the reversibility of the reaction and the effect of gas composition. These are dominating factors in plant practice and it is important to make adequate allowance for them. The alternative theory which is put forward below is based on the assumption that it is the *chemical reaction* in the interfacial region which controls the measured rate of absorption.

Chemical Kinetics Theory of Absorption Rate.—Considering for the moment absorption in acids more dilute than 30%, the present results can be represented with very fair accuracy by the simple relation

$$V = k_a[N_2O_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The calculated values of k_a are shown in col. 8 of Tables I and II and may be compared with the values of k_g. The coefficient of variation is rather smaller for k_a than for k_g (16% as compared to 21%) and also, which is more significant, the values of k_a do not show any systematic drift during the course of a run. (The results of the third, fourth, and fifth runs in Table II are, however, unsatisfactory in this respect.)

This linear relation between the absorption rate and the N_2O_4 concentration, or equally the square of the NO_2 concentration, indicates that the rate-limiting process may be a reaction involving one molecule of N_2O_4 or two molecules of NO_2, *e.g.*,

$$N_2O_4 + H_2O \longrightarrow HNO_3 + HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (C)$$

$$\text{or } 2NO_2 + H_2O \longrightarrow HNO_3 + HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (D)$$

If both reactions take place simultaneously, it would be expected that the absorption rate would be expressible by the relation

$$V = a[N_2O_4] + b[NO_2]^2$$

However, since $[N_2O_4] = K[NO_2]^2$, this equation can be reduced to either of the equivalent forms

$$V = k_a[N_2O_4] \text{ or } V = k_a'[NO_2]^2$$

The mean values of k_a and k_a' from the experimental data for the dilute acids are as follows:

$$\text{at } 25°,\ k_a = 1{\cdot}8 \times 10^{-2},\ k_a' = 3{\cdot}0$$

$$\text{at } 40°,\ k_a = 2{\cdot}3 \times 10^{-2},\ k_a' = 1{\cdot}3$$

The formulation of the reaction according to equation (C) thus gives a positive temperature coefficient, whilst formulation by equation (D) gives a negative coefficient. It seems likely, however, that reaction (C) takes place to the greater extent as it only involves a bimolecular collision. Expressed alternatively, the increase in the absorption rate at reduced temperatures (at the same concentration of total dioxide) is probably due to the increase in the proportion of the more reactive N_2O_4 rather than to any actual increase in the velocity coefficient. However, this is not an essential point in the present treatment.

Two further conclusions which may be drawn from the results on weak acids are: (*a*) k_a does not appear to depend on acid concentration; (*b*) there is no apparent effect of nitrous acid concentration, as shown in the fourth run of Table I. The absorption rate in dilute acids is thus determined almost entirely by the concentration of dinitrogen tetroxide in the gaseous phase, according to equation (4). However, with acids in the range 30—60% this simple relation no longer holds, and the measured absorption rate is found to become markedly dependent on the concentration of nitric oxide, and to a greater extent the stronger the acid. It is reasonable to attribute this effect to the increasing degree of reversibility of the reaction as the acid concentration is raised.

In the more concentrated acids we assume that the forward reaction continues to be proportional to the tetroxide concentration. A term for the reverse reaction is also introduced into the velocity equation and this term we take to be a power function of the NO and N_2O_4 concentrations:

$$V = k_a[N_2O_4] - \text{const. } [N_2O_4]^p[NO]^q$$

or

$$V = k_a\{[N_2O_4] - C[N_2O_4]^p[NO]^q\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

At equilibrium this equation must obviously reduce to the form $[NO]/[N_2O_4]^{3/2} = \text{const.}$, in accordance with the stoicheiometry of the overall process (A). This condition imposes a limitation on the choice of possible exponents in equation (5). The condition is clearly $(1 - p)/q = \frac{3}{2}$; for example, $p = 0$, $q = \frac{2}{3}$, or $p = \frac{1}{2}$, $q = \frac{1}{3}$, etc. Good correlation of the experimental data has been obtained by use of the latter pair of exponents, and this choice is also supported by the work of Abel (*Z. physikal. Chem.*, 1928, *A*, **132**, 55, 64; 1928, *A*, **134**, 279; 1928, *A*, **136**, 135, 419, 430; 1930, *A*, **148**, 337).

Abel and his collaborators carried out an exhaustive study on the rate of formation and decomposition of nitrous acid in the gas and the liquid phase system containing the species HNO_3, HNO_2, H_2O, NO, NO_2, N_2O_4, and N_2O_3. It was concluded that there are two elementary reactions in this system:

$$N_2O_4 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} HNO_2 + HNO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (C)$$

$$2HNO_2 \rightleftharpoons NO + NO_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (E)$$

It was found that (C) is slow and controls the overall rate, whilst (E) is relatively very rapid and can be regarded as being at equilibrium. In the experimental work the agitation of the bulk phases was vigorous and it appears that the diffusion of reactants across the gas–liquid interface did not affect the measured reaction rates. Abel was therefore able to treat the process as a normal example of chemical kinetics.

In the system studied by the present authors the same molecular species were present, and it is reasonable to suppose, therefore, that the *elementary reactions which took place were also the same*, i.e., Abel's reactions (C) and (E). The two systems differed only in the relative proportions of the different species, with the result that the overall process in Abel's system was the formation or decomposition of nitrous acid, and in our own system was the formation or decomposition of nitric acid. The compounding of the elementary reactions in the two cases is as follows :

$$4HNO_2 \rightleftharpoons 2NO + 2NO_2 + 2H_2O \quad \text{(E)}$$
$$N_2O_4 + H_2O \rightleftharpoons HNO_3 + HNO_2 \quad \text{(C)}$$
$$3HNO_2 \rightleftharpoons 2NO + HNO_3 + H_2O \quad \text{overall process}$$
$$2N_2O_4 + 2H_2O \rightleftharpoons 2HNO_3 + 2HNO_2 \quad \text{(C)}$$
$$2HNO_2 \rightleftharpoons NO + NO_2 + H_2O \quad \text{(E)}$$
$$3NO_2 + H_2O \rightleftharpoons 2HNO_3 + NO \quad \text{overall process} \quad \text{(A)}$$

As described above, Abel's evidence is that reaction (C) is rate-controlling and reaction (E) is relatively so rapid that it can be regarded as being at equilibrium. These conclusions agree well with our own observations; in dilute acids the absorption rate was proportional to the N_2O_4 concentration, as would be expected if reaction (C) controls the rate, and secondly, there was a rapid development of a steady state of coloration of the absorbing acid, corresponding to the setting up of the equilibrium (E).

We consider now the kinetics of the overall process (A) taking place in a *homogeneous* system. With reaction (C) as the rate-controlling step, and allowing for its reversibility, we obtain for the overall rate of the process the equation

$$\frac{-\,d(NO_2)}{dt} = \frac{3}{2}\{k_1[N_2O_4][H_2O] - k_2[HNO_3][HNO_2]\}$$

where k_1 and k_2 are the velocity constants of the forward and the reverse reaction. The symbol (NO_2) signifies the total concentration of NO_2 and N_2O_4 reckoned as NO_2. The factor $\frac{3}{2}$ allows for the reappearance of NO_2 by reaction (E).

The assumption of equilibrium of reaction (E) gives the relation

$$[HNO_2] = \text{const.} \times [NO_2]^{\frac{1}{2}}[NO]^{\frac{1}{2}}[H_2O]^{\frac{1}{2}}$$
$$= \text{const.} \times [N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}[H_2O]^{\frac{1}{2}}$$

Combining the two equations we have

$$\frac{-\,d(NO_2)}{dt} = \frac{3}{2}\{k_1[N_2O_4][H_2O] - \text{const.}\,[HNO_3][N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}[H_2O]^{\frac{1}{2}}\}$$
$$= \frac{3}{2}k_1[H_2O]\left\{[N_2O_4] - \frac{\text{const.}\,[HNO_3]}{k_1[H_2O]^{\frac{1}{2}}} \cdot [N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}\right\}$$
$$= k\{[N_2O_4] - C[N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}\} \quad (6)$$

where $k = \frac{3}{2}k_1[H_2O]$, and C depends on the concentration of the acid.

Equation (6) thus gives the rate of disappearance of dioxide in a homogeneous system containing the molecular species in question. This equation may also be expected to apply when there are two phases, gas and liquid, provided it is the chemical reaction which continues to determine the overall rate. This is the basic assumption of the present treatment.

The theory thus leads to an expression for the absorption rate identical with (6), except in so far as it is necessary to change the dimensions of constants, etc., to represent a rate per unit area instead of a rate per unit volume :

$$V = k_a\{[N_2O_4] - C[N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}\} \quad (7)$$

This equation is identical in form with equation (5) which was deduced on empirical grounds. At equilibrium the equation reduces to

$$[NO]_{eq.}/[N_2O_4]^{3/2}_{eq.} = 1/C^2$$

$$\therefore \quad [NO]_{eq.}/[NO_2]^3_{eq.} = K^{3/2}/C^2, \text{ where } K = [N_2O_4]/[NO_2]^2.$$

But $(p_{NO}/p^3_{NO_2})_{eq.} = K_1$, of which values are given in Fig. 2. Hence at temperature $t°$,

$$C = \frac{K^{\frac{1}{2}}}{K_1^{\frac{1}{3}}} \cdot \frac{273}{22{\cdot}4\,(273 + t)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The constant C can thus be calculated from equilibrium data and values are given in Table V. The numerical factor in equation (8) arises from the conversion of K_1 into units of concentration.

TABLE V.

Calculated Values of C, *the Constant in Equation* (7).

Acid concn., wt.-%.	Temp. 40°.			Temp. 25°.		
	K.	$\log_{10} K_1$.	$\log_{10} C$.	K.	$\log_{10} K_1$.	$\log_{10} C$.
40	56	3·05	−1·63	170	4·07	−1·75
50	56	1·96	−1·08	170	2·97	−1·20
60	56	0·89	−0·55	170	1·88	−0·66

The adequacy of equation (7) has been tested by evaluating k_a for each of the experimental measurements and the results are given in col. 9 of Tables I and II and col. 7 of Table III. It is seen that the values of k_a are generally fairly constant within any one experimental run, with the exception of three runs of Table II, where there was a systematic drift. With these exceptions, therefore, equation (7) gives a fairly good representation of the complex effect of gas composition on the absorption process. It also allows fully for the reversibility and it is particularly satisfactory that the equation, with the same value of k_a, can be applied whether NO_2 is being absorbed or evolved.*

Conclusions.—As shown in the previous section, the use of equation (7) gives a fairly good representation of the effect of the change in gas composition in any one experimental run, as shown by the approximate constancy of the calculated values of k_a. Between one run and another, however, there is appreciable variation of k_a, as shown by inspection of Tables I—III.

It is to be emphasised that the experimental method in use was not of the highest accuracy, but was primarily adapted to the exploration of the effect of wide ranges of gas composition. With this proviso in mind, Tables I—III show no evidence of a systematic effect on k_a either of acid flow rate or of acid concentration. On the other hand, there are indications of a small effect of gas velocity.

Chambers and Sherwood found evidence of a considerable dependence of absorption rate on the flow of gas and obtained the best treatment of their own data by taking the absorption rate as proportional to the 0·8 power of the Reynolds number (Re).† Taken on their own, the present

* It may be noted, however, that equation (7) is not satisfactory when the gaseous phase contains NO but no dioxide. This was the case at the commencement of the runs of Table III, for which the values of the evolution rate of NO_2, extrapolated to zero time, are shown in parentheses. Equation (7), and the mechanism of reactions (C) and (E), cannot account for the attack of pure NO on nitric acid, for which the probable reaction is

$$NO + HNO_3 \rightleftharpoons NO_2 + HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (F)$$

If it is assumed that reactions (C), (E), and (F) are operative simultaneously, equation (7) must be modified as follows:

$$V = k_a([N_2O_4] - C[N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}\} + k_f\left\{\frac{[N_2O_4]^{\frac{1}{2}}[NO]^{\frac{1}{2}}}{C} - [NO]\right\} \quad . \quad . \quad . \quad . \quad (9)$$

Rough values of k_f can be worked out from the zero-time data of Table III. These values are found to be about one-tenth of the value of k_a in 60% acid but are very much smaller in weaker acids. The result is that the second term in the above equation is generally much smaller than the first, except when NO is in great excess. Under normal conditions, equation (9) does not differ appreciably from equation (7), in its numerical value, and the simpler equation can therefore be used. This is equivalent to the neglect of the reaction (F).

† The Reynolds number is defined by

$$Re = vd\rho/\eta$$

where v, ρ, and η are the linear velocity, the density, and the viscosity respectively of the circulating gas, and d is the diameter of the absorption tower.

results do not provide very definite evidence, but the best correlation of both sets of results can probably be obtained by taking k_a as proportional to $Re^{0.5}$.* Alternatively, the variations in the present results may be due only to experimental error and not to any real effect of gas velocity.

It is to be noted also that the present experiments were conducted at low values of the linear rate of gas flow, such as obtain in nitrous gas absorption plants. In Chambers and Sherwood's work the Reynolds number was much higher (upwards of 1550, as compared to a maximum of 530 in the present experiments). The two sets of results are therefore not very comparable.

In conclusion, the object of the present work has been to investigate the effect on absorption rate of gas composition, acid concentration, and temperature, which are the most significant variables in plant practice. The main result has been to show that equation (7), which is derived from a chemical kinetic treatment of the absorption process, gives a satisfactory basis of interpretation. The equation accounts for the behaviour of wide ranges of gas composition on either side of the equilibrium point. The main effect of acid concentration is on the constant C of the equation, and the effect of temperature is on the constants C and k_a and on the relative proportions of NO_2 and N_2O_4. To this extent the present work may form a basis to which refinements may be added. There is undoubtedly scope for much further experimental work, particularly on the rate of absorption in acids more concentrated than 50% and on the effect of wide ranges of gas velocity.

We wish to express our thanks to Dr. M. P. Applebey for his interest and encouragement. Our thanks are also due to Mr. R. Forty for his careful assistance in the experimental work.

IMPERIAL CHEMICAL INDUSTRIES LTD.,
BILLINGHAM DIVISION, BILLINGHAM, CO. DURHAM. [*Received, August 26th*, 1946.]

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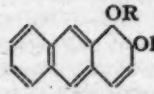
154. *The Metabolism of Polycyclic Compounds: the Configuration of the Dihydroxydihydroanthracenes produced from Anthracene.*

By E. BOYLAND and C. W. SHOPPEE.

The metabolism of carcinogenic and non-carcinogenic polycyclic hydrocarbons appears to conform to a general pattern. The configurations of the isomeric 1 : 2-dihydroanthracene-1 : 2-diols excreted by rats and rabbits respectively (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679) have therefore been investigated. The evidence now adduced shows that the isomeride from rats is either the *d*- or the *l-cis*-enantiomorph, but that the isomeride from rabbits is the optically inactive *dl-cis*-compound.

SOME years ago it was shown that anthracene fed to rats and rabbits is partly excreted in the urine as isomeric 1 : 2-dihydroanthracene-1 : 2-diols (I*a*) (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679) or as the *l*-glycuronic acid conjugates (I*b*) of these compounds (*idem*, *ibid.*, 1936, **30**, 728), and that all four substances are converted by dilute mineral acid into 1-hydroxyanthracene.



(I*a*; R = H)
(I*b*; R = $C_6H_9O_6$)

The structures of the diols (I*a*) were established by suitable oxidation and reduction experiments, but their configurations were not investigated.

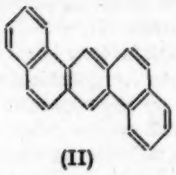
Subsequently, after having fed the carcinogen 1 : 2 : 5 : 6-dibenzanthracene (II) to rabbits,

* The mean values of k_a and $k_a/Re^{0.5}$ from Tables I—III are given below, together with the percentage root-mean-square deviations. The values of the same quantities calculated by application of equation (7) to the experimental data of Chambers and Sherwood are also given in the table. The deviation of

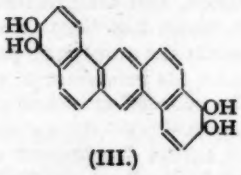
	$k_a \times 10^2$.	Devn., %	$k^2/Re^{0.5} \times 10^3$.	Devn., %
Present work: all acid concns. at 40°	1·9	24	1·1	10
,, ,, ,, 25°	1·6	16	0·8	13
Chambers and Sherwood: 8 results on acids up to 44% at 25°	3·3	25	0·6	19
,, ,, 4 ,, 50·7% acid at 25°	1·6	42	0·3	25
,, ,, 1 ,, 54·5% ,, ,,	1·0	—	0·2	—

$k_a/Re^{0.5}$ is seen to be rather smaller than the deviation of k_a; $k_a/Re^{0.5}$ is less satisfactory for the results as a whole. It may also be noted that Chambers and Sherwood's data show evidence of an effect of acid concentration on k_a or $k_a/Re^{0.5}$.

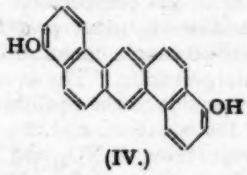
Boyland and Levi (*Chem. and Ind.*, 1938, **15**, 446) isolated a dihydroxy-derivative, also obtained by Dobriner, Rhoads, and Lavin (*Cancer Research*, 1942, **2**, 95; cf. Jones, *ibid.*, p. 245). Dobriner, Rhoads, and Lavin also isolated an apparently different dihydroxy-derivative from the urine and fæces of rats; this was later identified by Cason and Fieser (*J. Amer. Chem. Soc.*, 1940, **62**, 2681) as 4′ : 8′-dihydroxy-1 : 2 : 5 : 6-dibenzanthracene (IV). Boyland and Levi suggested that the production of (IV) might occur by way of an intermediate metabolite (III), analogous to (I*a*) or (I*b*), although no positive evidence for this was obtained. Fieser (Univ. of Pennsylvania Bicentennial Conference, 1940) also assumed that " perhydroxylation " of (II) precedes the metabolic formation of (IV) in rats and rabbits.



(II)

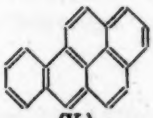


(III.)

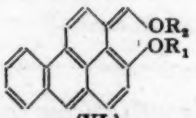


(IV.)

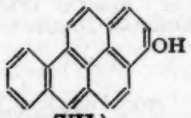
In the case of benzpyrene (V) fed to rats, it has been shown that the phenolic metabolite discovered by Chalmers and Crowfoot (*Biochem. J.*, 1941, **35**, 1270) is 8-hydroxybenzpyrene (VII) (Berenblum *et al.*, *Cancer Research*, 1943, **3**, 145, 151), whilst recently Weigert and Mottram (*ibid.*, 1946, **6**, 97, 109) have adduced evidence that here also metabolism proceeds by way of intermediates (VI) produced by " perhydroxylation ".



(V.)



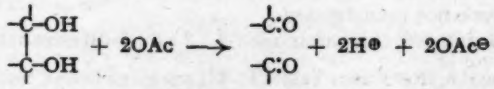
(VI.)



(VII.)

Thus it appears that an essential similarity exists between the metabolism of carcinogenic and non-carcinogenic polycyclic hydrocarbons. It is important to seek for some relation between the activity of a carcinogen and its metabolism because it is not known whether the change from a normal to an abnormal cell is induced by the hydrocarbon itself or by some locally produced derivative. Rats and rabbits metabolise ingested anthracene differently * (Boyland and Levi, *loc. cit.*); and it is known that rats and rabbits react differently to 1 : 2 : 5 : 6-dibenzanthracene—rats, but not rabbits, readily afford tumours at injection sites (Burrows and Boyland, *Amer. J. Cancer*, 1938, **32**, 367), which may conceivably be due to some difference in metabolism. It seemed therefore of possible value to attempt to determine the stereochemical configuration of the isomeric diols (I*a*), and an examination of these has now been made by one of us (C. W. S.) with material supplied by the other (E. B.).

Four isomeric 1 : 2-dihydroanthracene-1 : 2-diols can exist, comprising a pair of *cis*-enantiomorphs and a pair of *trans*-enantiomorphs. Since the isomerides described by Boyland and Levi were both optically active with specific rotations of $+16°$ and $-100°$, it appeared that the method of Criegee (*Ber.*, 1931, **64**, 260) would be diagnostic since it has been shown (Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159) that lead tetra-acetate invariably oxidises cyclic *cis*-1 : 2-diols much more rapidly than the *trans*-isomerides by a reaction which may be symbolised :



so that 1 mol. of diol requires 1 mol. of lead tetra-acetate. In applying this method to 1 : 2-dihydroanthracene-1 : 2-diols, it is necessary to take into consideration the reactivity of the *meso*-positions of the anthracene nucleus. K. H. Meyer (*Annalen*, 1911, **379**, 75) found that with 1 mol. of lead dioxide in acetic acid at 50° anthracene gives anthranyl acetate, whilst use of 2 mols. of lead dioxide at 70° affords *meso*-hydroxyanthranyl acetate which is stable to lead dioxide in acetic acid at 20°. Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1938, **60**, 1893) have shown that lead tetra-acetate in acetic acid is equivalent to the lead dioxide–acetic acid mixture used by Meyer and is a more convenient reagent; with N/10-lead tetra-acetate in acetic acid at 20°,

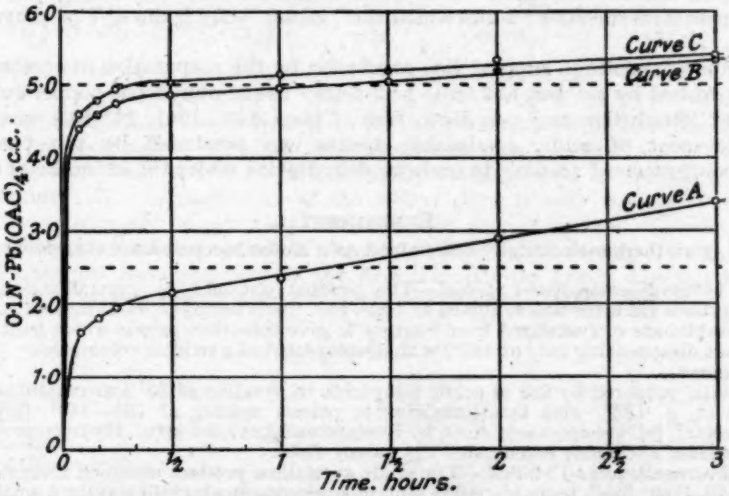
* Compare also Weigert and Mottram (*loc. cit.*) who state that it is certain that the metabolism of benzpyrene in rabbits is different from that in mice.

the main reaction would be expected to be the production of anthranyl acetate, which may be symbolised :

$$\gtrless CH + 2OAc \longrightarrow \gtrless C{\cdot}OAc + H^{\oplus} + OAc^{\ominus}$$

so that 1 mol. of anthracene should require 1 mol. of lead tetra-acetate. Curve *A* of the figure shows that this is in fact the case; under the conditions specified, anthracene undergoes fairly rapid oxidation by lead tetra-acetate to anthranyl acetate. The reaction is substantially complete in about 1 hour, and is followed by a further, slower oxidation, which probably represents the conversion of anthranyl acetate to *meso*-hydroxyanthranyl acetate.*

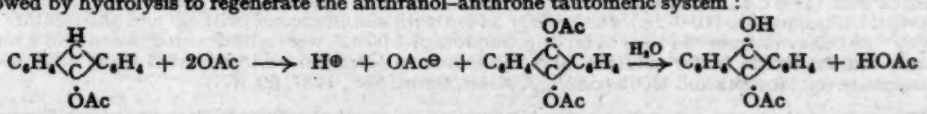
If the behaviour of anthracene towards lead tetra-acetate may be expected to be approximately reproduced in the corresponding oxidation under the same conditions of a 1 : 2-dihydroanthracene-1 : 2-diol, then 2 mols. of the reagent should be required. This is found to be so; curve *B* of the figure represents the oxidation of the " rat "-diol with N/10-lead tetra-acetate



in acetic acid at 20°, and curve *C* that of the " rabbit "-diol. The two curves are nearly coincident and show that an extremely rapid oxidation is succeeded by a slower, but still fairly fast, oxidation (analogous to that exhibited by anthracene, curve *A*), the process becoming substantially complete in about ½ hour and requiring 2 mols. of lead tetra-acetate; finally there occurs a further, much slower oxidation which is again analogous to that shown by anthracene.

It appears certain from the close similarity of the curves *B* and *C* that the two diols possess the same stereochemical configuration, and reasonably certain that this configuration must be *cis*- on account of the high speed with which oxidation occurs. Only two *cis*-1 : 2-diols, related as *d*- and *l*-forms, can exist, and these would be expected to possess approximately equal and opposite rotatory powers. Since this was not so according to the original observations of Boyland and Levi, specimens of the two diols were rigorously purified by sublimation in a high vacuum and subsequent crystallisation and their optical rotatory powers redetermined. The optical activity reported previously by Boyland and Levi for the " rat "-diol has been confirmed ($[\alpha]_D^{22°} -80° \pm 2°$), but the pure " rabbit "-diol has been found to be optically inactive. Boyland and Levi had reported only a small specific rotation ($[\alpha]_D^{20°} +16°$) for the " rabbit "-diol (they stated that it was not definitely proved that the substances they isolated were optically pure), and it may be noted that the specific rotation which they recorded for its dihydro-derivative

* The production of this compound is difficult to formulate; it seems likely that acetoxylation is followed by hydrolysis to regenerate the anthranol–anthrone tautomeric system :



This may be compared with the alcoholysis of tetraethyl 1-methyl-1 : 3-dicarboxyglutaconate to afford ethyl carbonate (Ingold and Thorpe, *J.*, 1919, 143) with regeneration of the three-carbon prototropic system :

$$(CO_2Et)_2C{=}CH{-}CMe(CO_2Et)_2 \xrightarrow{EtOH} (CO_2Et)_2C{=}CH{-}CHMe{\cdot}CO_2Et + CO(OEt)_2$$

($[\alpha]_D^{20°}$ $-1°$) and the diacetate of this ($[\alpha]_D^{20°}$ $-3°$) are within the limits of experimental error. The only earlier observations not satisfactorily accounted for are the physical constants of the " rabbit "-diol diacetate (reported to have m. p. 184°, $[\alpha]_D^{20°}$ 309°); whether prepared according to the directions of Boyland and Levi, or by use of acetic anhydide in pyridine at 20°, the pure diacetate has m. p. 120—122° (with indications of a polymorphic form, m. p. 131—132°), $[\alpha]_D^{22°}$ $0° \pm 2°$, and by alkaline hydrolysis regenerates the parent diol, m. p. 184°. A specimen of the crude crystalline diol, acetylated following the procedure of Boyland and Levi, furnished a crude diacetate, m. p. 120—121°, $[\alpha]_D^{22°}$ $+23° \pm 3°$. It was noticed that, whereas the " rat "-diol sublimed in a high vacuum leaving practically no residue, the " rabbit "-diol left a small carbonaceous deposit; it seems probable therefore that the small dextro-rotations shown by the crude crystalline " rabbit "-diol and diacetate are due to the presence of a small proportion of some substance of high dextro-rotatory power, such as the " rabbit "-diol-*l*-glyconuric acid ($[\alpha]_D^{20°}$ +195°) or some similar conjugate. It is to be concluded that the " rat "-diol is either *d*- or *l*-1 : 2-dihydroanthracene-*cis*-1 : 2-diol whilst the " rabbit "-diol is the *dl*-1 : 2-dihydroanthracene *cis*-1 : 2-diol.

An attempt was made to support this conclusion by the preparation of acetone compounds, which are furnished by *cis*- but not *trans*-1 : 2-diols; use of anhydrous copper sulphate as condensing agent (Reichstein and von Euw, *Helv. Chim. Acta*, 1941, **24**, 401) was unsuccessful, whilst employment of acidic condensing agents was precluded by the tendency of the 1 : 2-dihydroanthracene-1 : 2-diols to undergo dehydration under the influence of dilute mineral acid.

Experimental.

(All m. ps. were thermo-electrically determined on a Kofler block and are therefore corrected; limit of error $\pm 2°$.)

d(or *l*)-1 : 2-*Dihydroanthracene*-1 : 2-*diol*.—The product obtained by crystallisation from benzene of the material from rat urine was sublimed at 140—150° (bath temp.)/<0·001 mm. in a micromolecular still, and the sublimate recrystallised from benzene to give colourless prisms which melt partly at 162°, the last crystals disappearing only at 183°, with development of a reddish colouration; $[\alpha]_D^{22°}$ $-80° \pm 3°$ (*c*, 1·092 in dioxan).

The diacetate, prepared by use of acetic anhydride in pyridine at 20° and crystallised from ether–pentane, had m. p. 122°, with transformation to prisms melting at 139—143°, $[\alpha]_D^{22°}$ $-240° \pm 3°$ (*c*, 1·682 in dioxan), (cf. the constants given by Boyland and Levi, *loc. cit*). Hydrolysis with N/4-methyl alcoholic potassium hydroxide regenerated the parent diol.

dl-1 : 2-*Dihydroanthracene*-1 : 2-*diol*.—The crude crystalline product obtained from rabbit urine was sublimed at 150—160° (bath temp.)/<0·001 mm. in a micromolecular still leaving a small carbonaceous residue, and the sublimate recrystallised from benzene to yield colourless prisms, m. p. 184—186° to a reddish melt. The analysis specimen was dried at 60°/0·01 mm. and divided into two portions, one of these being used for the determination of the specific rotation; $[\alpha]_D^{22°}$ $0° \pm 3°$ (*c*, 1·123 in dioxan) (Found: C, 78·9; H, 5·7. Calc. for $C_{14}H_{12}O_2$: C, 79·3; H, 5·65%).

Diacetate. The pure diol (30 mg.) was dissolved in dry pyridine (0·3 c.c.), acetic anhydride (0·25 c.c.) added, and the mixture kept at 20° for 16 hours. Excess of the reagents was removed in a vacuum at 35°, the residue dissolved in ether, and the ethereal solution washed successively with 2N-hydrochloric acid, 2N-sodium carbonate, and water, then dried (Na_2SO_4), and evaporated. The faintly yellow crystalline product was purified by adsorption on a column of aluminium oxide (Merck–Brockmann, activity III—IV) prepared in pentane. Elution with benzene–pentane mixtures (up to 1 : 1) furnished the diacetate, which after recrystallisation from ether–pentane formed colourless thin prisms, m. p. 121—122°. The crystals were dried at 60°/0·01 mm. and a portion used for determination of the specific rotation: $[\alpha]_D^{22°}$ $0° \pm 2°$ (*c*, 0·991 in dioxan) (Found: C, 73·2, H, 5·2. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%); a further portion was hydrolysed with N/4-methyl-alcoholic potassium hydroxide to regenerate the parent diol, m. p. (crude) 184° (decomp.). Indications of a polymorphic form, m. p. 131—132°, of the diacetate were observed.

A specimen of the crude crystalline diol (50 mg.) was acetylated by refluxing with dry pyridine (0·3 c.c.) and acetic anhydride (0·25 c.c.) for ½ hour. After evaporation of excess of the reagents in a vacuum and evacuation to 0·01 mm. at 50°, the product was crystallised once from ether–pentane to give the diacetate in thin prisms, m. p. 120—122°, mixed m. p. 120—122° with the above preparation, $[\alpha]_D^{22°}$ $+23° \pm 4°$ (*c*, 2·32 in dioxan).

Oxidation with lead tetra-acetate. An N/10-solution of lead tetra-acetate in acetic acid (redistilled over chromium trioxide) (22·2 g./l.) was used; the substance to be oxidised (1/4000 mol.) was dissolved in acetic acid (10·0 c.c., redistilled over chromium trioxide) by warming and the solution cooled to 20°. N/10-Lead tetra-acetate (10·0 c.c.) was rapidly added with simultaneous swirling, and the mixture kept at 20°. At intervals from the time of mixing, aliquots of 1·00 c.c. were withdrawn and run into a sodium acetate–sodium iodide buffer solution, and the iodine so liberated was estimated using N/50 sodium thiosulphate (cf. Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1937, **59**, 377).

The authors desire to acknowledge the generous support of the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund, and the Anna Fuller Fund.

The Chester Beatty Research Institute,
The Royal Cancer Hospital (Free), London, S.W. 3. [*Received, August 8th*, 1946.

155. *Compounds related to Penicillic Acid. Part II. Synthesis of Dihydropenicillic Acid.*

By R. A. Raphael.

On the basis of ultra-violet light absorption measurements it is concluded that in solution penicillic acid possesses the lactol structure (II). The synthesis of dihydropenicillic acid (VIII) is described.

Penicillic acid, first isolated by Alsberg and Black (*U.S. Dept. Agric. Bureau Plant Ind. Bull.*, Nos. 199, 270) from *Penicillium puberulum* Bainier, and later by Birkinshaw, Oxford, and Raistrick (*Biochem. J.*, 1936, **30**, 394) from *P. cyclopium* Westling, has been assigned the tautomeric structures (I) and (II) by the latter authors.

(I.) (II.)

The hypothesis of this tautomeric system to explain the reactions of penicillic acid has now been shown to be unnecessary. The ultra-violet absorption spectra of the acid in both acid and alkaline solutions have been found to be practically identical and in complete accord with the lactol structure (II); the spectrum of the *methyl* ester is very similar (Table I). The presence of even a trace of the more highly conjugated keto-compound (I), which would be expected to exhibit maximal absorption at about 2700 A., would be easily detectable. Again, the compound obtained by saturation of the exocyclic double bond, dihydropenicillic acid (VIII), exhibits light absorption very similar to that of penicillic acid itself.*

Table I.

	Solvent.	$\lambda_{max.}$ A.	$\epsilon_{max.}$
Penicillic acid	0·02 M-KOH	2210	12,500
,, ,,	0·02 M-HCl	2280	11,500
Methyl penicillate	Alcohol	2260	20,000
Dihydropenicillic acid	0·02 M-KOH	2170	9,000
,, ,,	0·02 M-HCl	2270	14,000

It is noteworthy that no ketonic derivatives corresponding to structure (I) have been prepared, all the reagents employed giving compounds derived from the breakdown product of penicillic acid, 3 : 4-diketo-2-methylpent-1-ene (III).

(III.) (IV.)

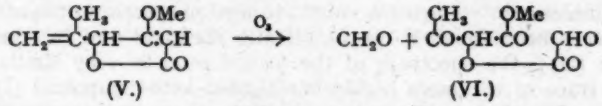
Further, the cyclic structure is compatible with the constitutions assigned to two other antibiotics, protoanemonin (Baer, Holden, and Seegal, *J. Biol. Chem.*, 1946, **162**, 65) and patulin (Gye *et al.*, *Lancet*, 1943, 625).

The starting material for the present synthetic investigation was technical methylallyl alcohol. This was oxidised by means of selenium dioxide to α-methylacraldehyde (Kautter, D.R.-P. 634,501), and the resulting aldehyde condensed with sodium acetylide in liquid ammonia to yield *iso*propenylethynylcarbinol (Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 87) in 73% yield. Carbonation of this *via* the disodium salt by the method of Zoss and Hennion (*J. Amer. Chem. Soc.*, 1941, **63**, 1151) produced a 68% yield of *3-hydroxy-4-methylpent-4-en-1-yne-1-carboxylic acid* (IV) [this yield is comparable with those recently obtained by Haynes and Jones (*J.*, 1946, 503) by carbonating the Grignard complexes of ethynylcarbinols]. The

* *Note added May 30th*, 1947.—After this paper had been submitted for publication, a communication appeared (Shaw, *J. Amer. Chem. Soc.*, 1946, **68**, 2510) in which the ultra-violet light absorption properties of penicillic acid were described. In aqueous solution the results were substantially in agreement with those reported above, but it was declared that, in 0·1N-sodium hydroxide, a new maximum at 2950 A. appeared; this was attributed to structure (I). In view of this, Dr. Braude has redetermined the light absorption of penicillic acid in 0·1N-sodium hydroxide. No sign of a maximum at 2950 A. was observed, the result being identical with that obtained above. Again, the American author himself reports that the light absorption properties of acetylacrylic acid, a compound structurally very similar to penicillic acid, are the same in both acid and alkaline solution, and are fully compatible with the lactol structure.

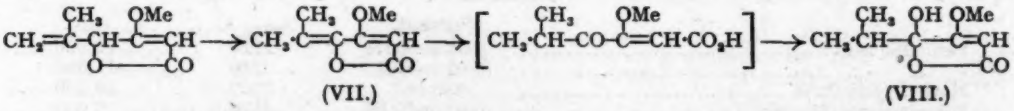
constitution of the acid was confirmed by complete hydrogenation to the lactone of 3-hydroxy-4-methylpentane-1-carboxylic acid, which was identified by its physical properties and by its conversion into the solid 3-bromo-4-methylpentane-1-carboxylic acid. Further characterisation was provided by the preparation of an *amide* and an S-*benzylisothiuronium* salt. The acid was easily convertible into its *methyl* ester by refluxing with methanolic sulphuric acid; both compounds had practically identical absorption spectra, thus showing that no anionotropic rearrangement had taken place during the esterification.

The methyl ester reacted vigorously with methanol in the presence of the boron trifluoride–mercuric oxide–trichloroacetic acid catalyst of Killian, Hennion, and Nieuwland (*inter alia*, *J. Amer. Chem. Soc.*, 1936, **58**, 80) to give a good yield of a neutral isomeric compound, m. p. 42—43°. Unlike the starting material it contained no active hydrogen and was unaffected by chromium trioxide solution even on warming; ready absorption of bromine in the cold showed that an unsaturated centre was present. These properties suggested that it was the *lactone* of 3-hydroxy-2-methoxy-4-methylpenta-1 : 4-diene-1-carboxylic acid (V), produced by addition of methyl alcohol to the triple bond of the acetylenic ester and subsequent elimination of the elements of methyl alcohol between the carbomethoxyl and the hydroxyl group. In confirmation of this structure ozonolysis of the compound yielded formaldehyde (identified as its dimedone derivative) and the ketone (VI) (characterised as its 2 : 4-*dinitrophenylhydrazone*).



(V.) (VI.)

Treatment of the lactone (V) with cold, dilute sodium hydroxide produced dihydropenicillic acid (VIII), identical with a specimen made by hydrogenation of natural penicillic acid. The production of dihydropenicillic acid is thought to be due to a prototropic change followed by fission of the lactone ring:



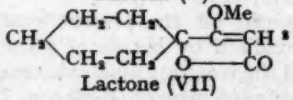
(VII.) (VIII.)

This mechanism is confirmed by the fact that use of a weaker base, ammonia, led to the formation of the *lactone* of 3-hydroxy-2-methoxy-4-methylpenta-1 : 3-diene-1-carboxylic acid (VII), which also yielded dihydropenicillic acid on hydrolysis. Ozonolysis of this lactone furnished a good yield of acetone 2 : 4-dinitrophenylhydrazone.

The correctness of the constitutions assigned to the two lactones is borne out by their ultra-violet absorption spectra (Table II).

TABLE II.

Absorption spectra determined in alcoholic solution.

	$\lambda_{max.}$, A.	$\epsilon_{max.}$		$\lambda_{max.}$, A.	$\epsilon_{max.}$
Acid (IV)	2150	4000	Lactone (V)	2210	13,000
Methyl ester of (IV)	2150	4000	 [2]	2210	15,500
Pr·CH(OH)·C≡C·CO_2H [1]	2150	4500	Lactone (VII)	2700	23,000

[1] Haynes and Jones, *loc. cit.* [2] Jones and Whiting, private communication.

Further work along these lines, aiming at the ultimate synthesis of penicillic acid, is being continued.

EXPERIMENTAL.

3-Hydroxy-4-methylpent-4-en-1-yne-1-carboxylic Acid (IV).—To a solution of sodamide (from sodium, 11·5 g.) in liquid ammonia (1 l.) was added *iso*propenylethynylcarbinol (24 g.) in dry ether (20 c.c.). The ammonia was allowed to evaporate overnight; more dry ether was introduced and dry nitrogen passed through to remove all traces of ammonia. A large excess of solid carbon dioxide was then added. When the reaction mixture had warmed to room temperature, dilute sulphuric acid was run in to decompose the sodium salt, and the ethereal layer was removed and extracted with dilute sodium carbonate solution. The sodium carbonate was acidified and the precipitated acid extracted with ether; the ethereal extract was washed with water and dried ($MgSO_4$). Evaporation of the ether yielded a viscous oil which soon solidified, crystallisation from benzene yielding the required *acid* (23·8 g.; 68%) in nacreous plates, m. p. 80—81° (Found: C, 61·2; H, 5·5; equiv., 142. $C_7H_8O_3$ requires C, 60·0; H, 5·8%; equiv.,

140). The S-*benzylisothiuronium* salt crystallised from a small volume of alcohol in needles, m. p. 156—157° (decomp.) (Found: N, 9·0. $C_{15}H_{18}O_3N_2S$ requires N, 9·1%).

Hydrogenation.—The above acid was fully hydrogenated in ethyl acetate solution using platinic oxide as catalyst. After removal of catalyst and solvent the residual lactone of 3-hydroxy-4-methylpentane-1-carboxylic acid had b. p. 106—108°/20 mm., $n_D^{20°}$ 1·4390 (Linstead and Rydon, *J.*, 1933, 584, give b. p. 98°/15 mm., $n_D^{20°}$ 1·4410). Reaction of the lactone with hydrogen bromide yielded 3-bromo-4-methylpentane-1-carboxylic acid, which crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 40—41° (Boorman, Linstead, and Rydon, *J.*, 1933, 576, give m. p. 41°).

Methyl 3-hydroxy-4-methylpent-4-en-1-yne-1-carboxylate. The acid (9 g.) was refluxed overnight with dry methanol (35 c.c.) and sulphuric acid (*d* 1·84; 0·4 g.). The cooled solution was poured into water and the product isolated by means of ether. Distillation furnished the *ester* as a mobile oil, b. p. 125°/9 mm., $n_D^{17°}$ 1·4820 (Found: C, 61·7, 61·8; H, 6·6, 6·5; OMe, 20·4. $C_8H_{10}O_3$ requires C, 62·2; H, 6·6; OMe, 20·1%).

3-Hydroxy-4-methylpent-4-en-1-yne-1-carboxyamide. The above ester (5 g.) was shaken with aqueous ammonia (*d* 0·88; 20 c.c.) until the mixture became homogeneous. Next day the solution was evaporated to dryness under reduced pressure and the residue extracted with boiling toluene; much glassy material remained undissolved. On cooling the toluene solution, needles of the *amide* (1·8 g.), m. p. 105—106°, separated (Found: C, 60·2; H, 6·4; N, 10·4. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%)

Lactone of 3-Hydroxy-2-methoxy-4-methylpenta-1 : 4-diene-1-carboxylic Acid (V).—The acetylenic ester (5 g.) was slowly dropped into dry methanol (15 c.c.) containing red mercuric oxide (0·1 g.), boron trifluoride–ether complex (0·1 c.c.), and trichloroacetic acid (10 mg.). After the initial exothermic reaction had subsided, the mixture was kept for 3 hours and then poured into sodium hydrogen carbonate solution, and the precipitated oil was extracted with ether. Drying and evaporation of the ether yielded a pale yellow liquid, b. p. 140°/9 mm., which solidified to a crystalline mass, m. p. 42—43° (3·2 g.; 64%) (Found: C, 62·1, 61·8; H, 6·5, 6·6; OMe, 20·2; *M* [ebull. in acetone], 149. $C_8H_{10}O_3$ requires C, 62·2; H, 6·6; OMe, 20·1%; *M*, 154). The *compound* showed no active hydrogen (Zerewitinoff). It absorbed bromine rapidly in the cold but was unaffected by chromium trioxide solution even on warming.

Ozonolysis. The lactone (V) (1 g.) was dissolved in purified acetic acid (10 c.c.) and ozonised oxygen passed through until absorption ceased (6 hours), the issuing gases being bubbled through water to trap volatile products. The wash water was poured into the acetic acid solution, zinc dust (5 g.) added, and the mixture heated to boiling in a stream of nitrogen, the issuing gases being passed into a saturated aqueous alcoholic solution of dimedone. By next day the solution had deposited needles of the dimedone compound of formaldehyde (680 mg.; 36%), m. p. 190—191° after crystallisation from aqueous alcohol, undepressed on admixture with an authentic specimen,

The original solution was filtered from zinc dust and treated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. The heavy yellow precipitate (1·3 g.; 54%) was filtered off, dried, and crystallised from nitrobenzene; yellow needles, m. p. 232—233° (decomp.) (Found: N, 15·4; OMe, 8·5. $C_{13}H_{12}O_6N_4$ requires N, 15·2; OMe, 8·4%). The analysis corresponds to that of the 2 : 4-*dinitrophenylhydrazone* of the ketone (VI).

Dihydropenicillic Acid (VIII).—The lactone (V) (1·5 g.) was dissolved in methanol (10 c.c.), N-sodium hydroxide (11 c.c.; 1·1 mols.) added, and the mixture left overnight. The methanol was evaporated under reduced pressure and the solution acidified with dilute sulphuric acid. Isolation by means of ether furnished an acidic solid (800 mg.) which did not decolourise bromine and crystallised in needles, m. p. 85—86°, from light petroleum (b. p. 60—80°) containing a few drops of benzene (Found: C, 55·5; H, 7·0; OMe, 18·25. Calc. for $C_8H_{12}O_4$: C, 55·75; H, 7·0; OMe, 18·0%). Dihydropenicillic acid, prepared from natural penicillic acid by hydrogenation (Birkinshaw, Oxford, and Raistrick, *loc. cit.*), crystallised from the same solvent in needles, m. p. 84—85°. A mixture of the two products showed no depression in m. p.

The action of diazomethane on the synthetic compound, followed by alcoholic hydrazine hydrate, gave, after 8 days, clumps of the orthodiazine, m. p. 210—211° after crystallisation from benzene. This m. p. was undepressed on admixture with the compound prepared in a similar way from the natural acid (Birkinshaw, Oxford, and Raistrick, *loc. cit.*).

Lactone of 3-Hydroxy-2-methoxy-4-methylpenta-1 : 3-diene-1-carboxylic Acid (VII).—The lactone (V) (1 g.) was dissolved in methanol (3 c.c.), and aqueous ammonia (*d* 0·880; 0·5 c.c.) added. Next day the light brown liquid was poured into water; the precipitated oil quickly solidified, and the crystalline mass (800 mg.) was filtered off, washed with water, and dried. The *lactone* crystallised from light petroleum (b. p. 60—80°) in prisms or needles, m. p. 76—78° (Found: C, 62·3; H, 6·4; OMe, 20·2. $C_8H_{10}O_3$ requires C, 62·2; H, 6·6; OMe, 20·1%). The compound showed no active hydrogen (Zerewitinoff).

Hydrolysis with sodium hydroxide as described for the lactone (V) again furnished dihydropenicillic acid.

Ozonolysis. Lactone (VII) was treated as described for (V). The issuing gases from the decomposition of the ozonide were led into excess of alcoholic 2 : 4-dinitrophenylhydrazine sulphate. Next day the orange precipitate (960 mg.; 66%) was filtered off; after crystallisation from alcohol the derivative had m. p. 124—126° undepressed on admixture with an authentic specimen of acetone 2 : 4-dinitrophenylhydrazone.

Methyl Penicillate (prepared by Dr. J. O. Harris).—A mixture of penicillic acid (1 g.), methyl iodide (2 c.c.), anhydrous potassium carbonate (1 g.), and dry acetone (10 c.c.) was refluxed for 4 hours; the cooled solution was filtered and evaporated to dryness, and the residue extracted with ether. Evaporation of the ether furnished the *ester* as a pale yellow oil (800 mg.; 73%), b. p. 100—110° (bath temp.)/0·05 mm., $n_D^{28°}$ 1·4853. It solidified to colourless prisms, m. p. 35° (Found: C, 58·6; H, 6·3; OMe, 31·3. $C_9H_{12}O_4$ requires C, 58·65; H, 6·55; OMe, 33·6%).

The author thanks Dr. E. A. Braude for the absorption data and Mr. S. Bance, B.Sc., A.R.I.C., for the semimicroanalyses. He is also indebted to Dr. A. J. Ewins, F.R.S., Professor H. Raistrick, F.R.S.,

Dr. J. N. Ashley, and Dr. E. R. H. Jones for their interest in this work and to the Directors of Messrs. May & Baker Ltd. for permission to publish the results.

The penicillic acid employed in the above investigations was provided by courtesy of Professor Raistrick.

THE RESEARCH LABORATORIES, MAY AND BAKER LTD.,
DAGENHAM.

[*Received, October 3rd*, 1946.]

156. *Cinnolines. Part XII. 4-Methylcinnolines.*

By C. M. ATKINSON and J. C. E. SIMPSON.

The preparation of 4-methylcinnolines is described. Conversion of these substances into 4-*p*-dimethylaminostyryl-1-ethylcinnolinium iodides discloses activity of the 4-methyl group, and indicates that N^1 is the basic centre in these compounds.

AN important aspect of cinnoline chemistry—and one which exemplifies what is still largely an unexplored problem in relation to polynitrogenous ring-systems in general—is the question of the location of the basic centre of the heterocyclic nucleus. Busch and Rast (*Ber.*, 1897, **30**, 521) stated that the parent substance, cinnoline (I), is a strong base, and it might therefore be supposed, from analogy with the difference in basicity between *iso*quinoline and quinoline, that N^2 and not N^1 participates in the formation of salts of cinnoline derivatives. However, it was by no means certain that mere casual comparisons of this type would prove reliable, and more direct chemical evidence was therefore sought.

As one line of attack, a study has been made of the effect of substitution at C^4 on the ease with which various cinnoline bases may be converted into quaternary salts, together with an investigation of the alkaline decomposition of the salts so formed. A discussion of this work is reserved for a later paper in this series, and in the present communication we describe preliminary results obtained from an alternative approach to the problem, namely the preparation and study of 4-methylcinnolines (II). Compounds of this type should exhibit the methyl-group reactivity characteristic of quinaldines or lepidines if N^1 is the basic centre, but not if N^2 is the point of maximum electron availability.

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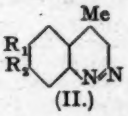
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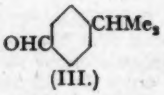
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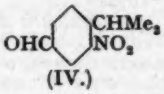
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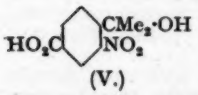
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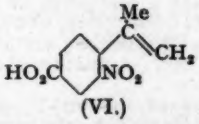
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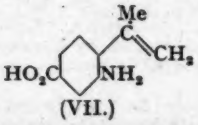
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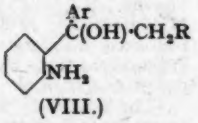
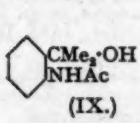

(VIII.)

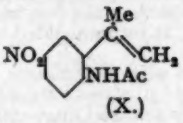
The only example of a 4-methylcinnoline in the literature is the 7-carboxylic acid (II; $R_1 = H$; $R_2 = CO_2H$), prepared by Widman (*Ber.*, 1884, **17**, 722) from cuminal (III) *via* the intermediates (IV—VII). In repeating this work we found that the crude acid was most conveniently purified through the *ethyl* ester (II; $R_1 = H$; $R_2 = CO_2Et$). Although each stage of the synthesis proceeded reasonably smoothly, the cost of the starting material renders the compound somewhat inaccessible in quantity, and we therefore turned our attention to the preparation of other 4-methylcinnolines.

We have found that *o-iso*propenylanilines can be readily prepared by the action of methylmagnesium iodide on anthranilic methyl esters or *o*-aminoacetophenones, followed by dehydration of the resultant carbinols with phosphoric anhydride. These carbinols were surprisingly resistant to hot dilute sulphuric acid, in contrast to the ease with which diarylcarbinols of type (VIII) can thus be dehydrated (Stoermer and Fincke, *Ber.*, 1909, **42**, 3115; Stoermer and Gaus, *ibid.*, 1912, **45**, 3104; Simpson and Stephenson, *J.*, 1942, 353; Simpson, *J.*, 1943, 447; 1946, 673); for example, *o*-aminophenyldimethylcarbinol remained unchanged unless conditions were so severe as to produce sulphonation. On the other hand, the carbinol (V) is smoothly dehydrated by cold concentrated sulphuric acid, and according to Widman the amine derived from (V) also can be easily dehydrated. This contrast between the behaviour of our monoaryl-carbinols prepared from *o*-aminoacetophenones and that of the monoaryl-carbinol (V) and compounds of type (VIII) suggested that the introduction of

electron-attractive groups into the aniline nucleus might facilitate dehydration, and would in any event be expected to retard sulphonation. Accordingly the *substance* (IX) was nitrated;



(IX.)



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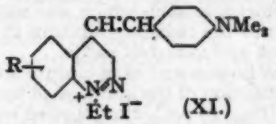

(XI.)

the product, obtained in rather poor yield, gave analytical data indicating that dehydration had accompanied nitration, and is therefore probably 2-(*5-nitro-2-acetamidophenyl*)*propylene* (X). The reaction did not seem to be readily adaptable to large-scale work, and for this reason, and also because the phosphoric anhydride method appeared to be of general applicability, this approach was not further investigated.

Diazotisation of the *o-iso*propenylanilines yielded the corresponding cinnolines, and by this method we prepared * 4-*methyl*- (II; $R_1 = R_2 = H$), 6-*chloro*-4-*methyl*- (II; $R_1 = Cl$, $R_2 = H$), and 7-*chloro*-4-*methyl-cinnoline* (II; $R_1 = H$, $R_2 = Cl$). Two noteworthy features of these reactions were, first, that appreciable amounts of strongly-coloured green or blue substances are produced (this does not occur during the formation of 4-hydroxycinnolines or of 4-arylcinnolines), and, secondly, that the cyclisations are considerably faster than those which yield 4-hydroxycinnolines. The favourable influence on cinnoline-formation of an α-methyl group in the aminoethylene, in contrast to the inhibitory effect of an α-hydrogen atom (*J.*, 1946, 673), gives additional support to the mechanism previously advanced for the Widman–Stoermer reaction (Schofield and Simpson, *J.*, 1945, 520), and would seem to be due to the hyperconjugative effect of the methyl group.

Condensation of the *ethiodides* of the 4-methylcinnolines with *p*-dimethylaminobenzaldehyde proceeded in the absence of a catalyst, giving the corresponding 4-p-*dimethylaminostyryl*-1-*ethylcinnolinium iodides* (as XI); these substances were blue dyes, which were, however, fugitive to acid and strong alkali. It is clear that quaternary-salt formation confers high reactivity on the 4-methyl group, and the quaternary nitrogen in these compounds is accordingly N^1 and not N^2. It may well be that N^1 is the basic centre of all simple cinnolines which may be prepared by the three standard synthetic routes so far available (Schofield and Simpson, *loc. cit.*), because these reactions of necessity give rise to derivatives, containing a 4-substituent, which may be regarded as exercising a controlling influence on the availability of electrons at N^1. Further evidence, however, is required before any statement can be made regarding the basic centre in compounds unsubstituted at C^4, *e.g.*, cinnoline itself and the 3-hydroxycinnoline mentioned (without details) by Neber, Knöller, Herbst, and Trissler (*Annalen*, 1929, 471, 113); the preparation and study of 3-methylcinnolines should be illuminating in this respect.

Experimental.

(Melting points are uncorrected.)

Preparation of 4-Methylcinnoline-7-carboxylic Acid.—The following conditions were evolved from the early literature. Cuminal (50 g.) was added during 40 minutes to a mixture of nitric acid (230 c.c., *d* 1·52) and concentrated sulphuric acid (260 c.c.) at 0—5° with mechanical stirring. The solution was allowed to reach 10° by removal from the freezing mixture and poured on ice (2·5 kg.), and the crude 3-nitro-4-*iso*propylbenzaldehyde purified by digestion with aqueous sodium carbonate and water; yield, 63·5 g. (97%), m. p. 51° (Widman, *Ber.*, 1882, **15**, 166, gives m. p. 54° for the recrystallised compound). Although comparable yields were obtained in five consecutive runs, the reaction is capricious, as several later experiments gave only 60% yields of crystalline product (acids of different origin were used in these experiments, but the conditions were otherwise seemingly identical in the two series). The nitro-aldehyde (20 g., m. p. 50—51°) was refluxed with aqueous potassium permanganate (5%, 2 l.), added in portions during 10—12 hours. The product obtained by concentration and acidification of the filtered solution was usually almost pure 3-nitro-4-(1-hydroxy*iso*propyl)benzoic acid (yield, *ca.* 50%; m. p. 185—187°; Widman, *Ber.*, 1882, **15**, 2547, gives m. p. 190—191°), but occasionally it was contaminated with 3-nitro-4-*iso*propylbenzoic acid, m. p. 158° (lit. m. p., 157—158°) (Found: C, 53·5; H, 5·0. Calc. for $C_{10}H_{11}O_4N$: C, 53·3; H, 4·9%), which was readily removed from the crude product by extraction with benzene. The hydroxy-acid (20 g.) was added during ½ hour to concentrated sulphuric acid (100 c.c.); after a further hour, the clear solution was poured on ice, and 3-nitro-4-*iso*propenylbenzoic acid (13·8 g., 75%), m. p. 153—154° (lit. m. p., 154—155°), isolated by dissolution of the crude product in aqueous sodium hydroxide, acidification, and crystallisation from aqueous alcohol. A solution of this substance (5 g.) in ammonia (*d* 0·88, 2 c.c.; water, 14 c.c.) was added with shaking during 10 minutes to a suspension prepared from ferrous sulphate (50 g.), water (100 c.c.), and ammonia

* In an article which appeared after this paper had been prepared for publication, Jacobs, Winstein, Henderson and Spaeth (*J. Amer. Chem. Soc.*, 1946, **68**, 1310) describe the preparation of 4-methylcinnoline by a similar route, and, *inter alia*, its condensation with benzaldehyde.

(*d* 0·88, 25 c.c.); after being heated on the steam-bath for ½ hour, the solution was filtered and the filtrate and washings were concentrated (reduced pressure) to 250 c.c. Addition of concentrated hydrochloric acid (150 c.c.) precipitated the hydrochloride (4·4 g.), m. p. 240° (decomp.), of 3-amino-4-*iso*propenylbenzoic acid, which was more easily handled than the free amino-acid (needles, m. p. 93—94°). Addition of the reducing mixture to the nitro-acid, as recommended by Widman (*Ber.*, 1883, **16**, 2567), gave poor and variable yields.

Diazotisation and ring-closure was best effected with a minimum amount of acid (cf. Widman, *loc. cit.*); a solution of the amino-acid hydrochloride (5 g.) in water (50 c.c.) was treated with aqueous sodium nitrite (10%, 18 c.c.), the solution being kept barely acid to Congo-red with hydrochloric acid. After 1 hour at room temperature no coupling reaction with β-naphthol could be obtained; the crude cinnoline acid [4·2 g., m. p. 235° (decomp.)] was collected and purified by crystallisation, or preferably *via* the ester, as follows. A suspension of the acid (9·1 g.) in alcohol (90 c.c.) was saturated with dry hydrogen chloride; the clear blue solution was refluxed for ½ hour and then again saturated at room temperature. Most of the alcohol was driven off and the ester isolated by treatment with excess of aqueous sodium carbonate and extraction with ether, from which *ethyl 4-methylcinnoline-7-carboxylate* (7 g.) separated in golden plates, m. p. 117° (leaflets from hot water) (Found: C, 67·1; H, 5·7; N, 13·1. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). Hydrolysis of the ester (3 g.) with aqueous potassium hydroxide (10%, 60 c.c.) (3 hours' reflux) and acidification with acetic acid (50%, 40 c.c.) gave 4-methylcinnoline-7-carboxylic acid (2·5 g.), which formed almost colourless needles, m. p. 251—253° (decomp.), from alcohol [Widman, *loc. cit.*, gives m. p. 230° (decomp.)] (Found: C, 63·8; H, 4·4; N, 15·25. Calc. for $C_{10}H_8O_2N_2$: C, 63·8; H, 4·3; N, 14·9%), very sparingly soluble in water and aqueous sodium phosphate, but fairly easily soluble in dilute hydrochloric acid and in saturated aqueous sodium acetate.

Reaction between 4-Methylcinnoline-7-carboxylic acid and o-*Nitrobenzaldehyde.*—A mixture of *o*-nitrobenzaldehyde, the acid, anhydrous zinc chloride (1·5 g. of each), and acetic acid (6 c.c.) was heated slowly to 120° and maintained at this temperature for 1 hour. The mixture was digested with warm hydrochloric acid (25 c.c., 2N) and the solid material [1·2 g., m. p. 283—285° (decomp.)] filtered off, washed, and crystallised from acetic acid, giving deep yellow micro-crystals, m. p. 285° (decomp.), insoluble in aqueous sodium carbonate or hydroxide (Found: C, 61·5; H, 3·9; N, 12·85. $C_{17}H_{11}O_4N_3,\frac{1}{2}H_2O$ requires C, 61·8; H, 3·65; N, 12·7%). The product from another experiment formed greenish micro-crystals, m. p. 297—298° (without decomp.), which did not depress the m. p. of the foregoing material (Found: C, 62·55; H, 3·45; N, 13·3, 13·25%).

Preparation of o-iso*Propenylanilines.*—(*a*) A solution of methyl anthranilate (50 g.) in ether (500 c.c.) was added with stirring during ¾ hour to methylmagnesium iodide [from magnesium (40 g.), methyl iodide (240 g.), and ether (750 c.c.)]. After ½ hours' refluxing, the product was decomposed with iced ammoniacal ammonium chloride, and the oily carbinol (53 g.) isolated by ether-extraction. The same yield of carbinol resulted from similar manipulation of *o*-aminoacetophenone (10 g.) in ether (80 c.c.) and methylmagnesium iodide [from magnesium (10 g.), methyl iodide (54 g.), and ether (150 c.c.)]. Acetylation of each sample (cold acetic anhydride) gave *o-acetamidophenyldimethylcarbinol*, which formed small colourless needles, m. p. 146—147°, from benzene–ligroin (b. p. 40—60°) (Found: C, 68·0; H, 7·65; N, 7·2. $C_{11}H_{13}O_2N$ requires C, 68·4; H, 7·8; N, 7·25%). Addition of this substance (0·5 g.) during ½ hour to a mixture of nitric acid (*d* 1·487) and concentrated sulphuric acid (5 : 2, v/v, 3 c.c.) at − 15° gave a clear solution which was poured on ice after a further ½ hour; the crude product obtained by basification with ammonia was crystallised from aqueous alcohol and from ligroin (b. p. 40—60°), yielding lustrous yellow leaflets (0·34 g., m. p. 88—89°) of *2-(5-nitro-2-acetamidophenyl)-propylene* (Found: C, 60·2; H, 5·6; N, 13·05. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%). *o*-Aminophenyldimethylcarbinol (30 g.) was dehydrated with phosphoric anhydride (60 g.) in benzene (300 c.c.) under reflux (3 hours). The solution was poured on ice, the gummy residue made alkaline with ammonia, and the whole extracted with ether, yielding crude *o-iso*propenylaniline as an oil (28 g.).

(*b*) Methyl 4-chloroanthranilate was obtained in 68% yield by the following improvement of Hunn's method (*J. Amer. Chem. Soc.*, 1923, **45**, 1024). A cold suspension of the acid (100 g.) in methyl alcohol (98%, 1 l.) was saturated with dry hydrogen chloride; after 1 hour's refluxing, the solution was again saturated at room temperature, concentrated, and poured into excess of dilute aqueous ammonia. The ester formed colourless needles, m. p. 68—70° (Hunn gives m. p. 68·5°) after crystallisation from ligroin (b. p. 60—80°). Treatment of the ester (30 g.) in ether (300 c.c.) with methylmagnesium iodide [from magnesium (20 g.), methyl iodide (115 g.), and ether (500 c.c.)] as above yielded the crude *o*-amino-carbinol (30 g.) as an oil, which with cold acetic anhydride gave the N-*acetyl* derivative (colourless prisms from benzene), m. p. 151—153° (Found: C, 58·15; H, 6·1. $C_{11}H_{14}O_2NCl$ requires C, 58·0; H, 6·2%). Dehydration of the amino-carbinol (28 g.) as above gave an oil (26 g.), which on treatment with hot acetic anhydride, followed by decomposition and isolation of the product with ether, yielded *2-(4-chloro-2-acetamidophenyl)propylene* as colourless polyhedra, m. p. 68—70° after crystallisation from ligroin (b. p. 40—60°) (Found: C, 63·0; H, 5·35. $C_{11}H_{12}ONCl$ requires C, 63·0; H, 5·8%).

(*c*) Treatment of 5-chloro-2-aminoacetophenone (20 g.; Simpson *et al.*, *J.*, 1945, 646) in ether (300 c.c.) with methylmagnesium iodide [from magnesium (13 g.), methyl iodide (80 g.), and ether (400 c.c.)] as above gave *5-chloro-2-aminophenyldimethylcarbinol* (19 g.), which formed yellow needles, m. p. 83—84°, from ether–ligroin (b. p. 40—60°) (Found: C, 58·3; H, 6·35; N, 8·65. $C_9H_{12}ONCl$ requires C, 58·2; H, 6·5; N, 7·5%). The N-*acetyl* derivative (cold acetic anhydride), m. p. 136—137°, formed colourless micro-crystals from benzene–ligroin (b. p. 40—60°) (Found: C, 58·65; H, 6·2. $C_{11}H_{14}O_2NCl$ requires C, 58·0; H, 6·2%), and the N-*benzoyl* derivative (pyridine–benzoyl chloride) crystallised from aqueous alcohol in small colourless prisms, m. p. 148—153° (this extended melting point seemed to be characteristic of the substance) (Found: C, 66·3; H, 5·5; N, 5·2. $C_{16}H_{14}O_3NCl$ requires C, 66·3; H, 5·6; N, 4·8%). The amino-carbinol (12 g.) and sulphuric acid (18N, 160 c.c.) were heated for 1 hour on the steam-bath. Dilution with water, basification, and extraction with ether gave 2-(5-chloro-2-aminophenyl)propylene as an oil (12 g.); the N-*benzoyl* derivative separated from aqueous alcohol in fine colourless needles, m. p. 126—127° (Found: C, 71·4; H, 5·4; N, 5·65. $C_{16}H_{14}ONCl$ requires C, 70·7; H, 5·2; N, 5·15%).

Preparation of 4-Methylcinnolines from o-isoPropenylanilines.—(*a*) The crude product prepared in (*a*) above (12 g.) was dissolved in hydrochloric acid [concentrated acid (20 c.c.) and 2N acid (80 c.c.)] and a small amount of insoluble oil removed with ether. The suspension obtained by cooling the acid solution to 5° was diazotised with solid sodium nitrite (5·1 g.); a clear, deep green solution was formed, and on being warmed to 60° the coupling reaction became negative and the colour changed to red. Addition of saturated aqueous sodium acetate precipitated an oil which was collected with ether; the extract, after being washed with sodium hydroxide and water, was dried and concentrated, and the bright green residue repeatedly extracted with hot ligroin (b. p. 60—80°), from which 4-methylcinnoline separated in slender yellow needles, m. p. 74—75° (yield, 6 g.) [Jacobs *et al.* (*loc. cit.*) give m. p. 72·5—74°] (Found: C, 74·9; H, 5·35; N, 20·0. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6; N, 19·45%), moderately soluble in ether, and easily in water and ethanol. The recrystallised base gave a deep red solution in dilute hydrochloric acid, but the colour was apparently due to traces of impurity, as material recovered from oxidation with permanganate (*q.v.*) no longer gave this colour. *4-Methylcinnoline picrate*, prepared in alcoholic solution, formed fern-like aggregates of green needles, m. p. 179—180° (Found: C, 48·05; H, 2·85. Calc. for $C_{15}H_{11}O_7N_5$: C, 48·25; H, 3·0%) [Jacobs *et al.* (*loc. cit.*) give m. p. 176—177°]. Treatment of 4-methylcinnoline methosulphate with diazotised aniline in faintly alkaline medium (cf. Koenigs and Bueren, *J. pr. Chem.*, 1936, **146**, 119) gave a purple amorphous product which could not be purified either as the salt or as the dye base.

(*b*) A solution of the olefin (20 g.) described in (*b*) above in hydrochloric acid (2N, 160 c.c.) was diazotised with solid sodium nitrite (6·2 g.); *7-chloro-4-methylcinnoline* (11·7 g.), isolated and purified as in the preceding paragraph, crystallised from ligroin (b. p. 60—80°) in minute yellow leaflets, m. p. 119—120° (Found: C, 60·1; H, 4·0; N, 15·35. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·9; N, 15·7%).

(*c*) The suspension of hydrochloride obtained by mixing crude 2-(5-chloro-2-aminophenyl)propylene (12 g.) and hydrochloric acid (50 c.c., 6N) was diazotised with aqueous sodium nitrite (10%, 48 c.c.). On heating to 70°, an intense purple colour developed, and the coupling power of the solution rapidly disappeared. The solution was filtered from some purple-black tar, which was extracted with warm dilute hydrochloric acid, and filtrate and washings were then treated with excess of sodium acetate. Treatment as above gave the crude cinnoline (5·7 g., m. p. 123—128°), which was purified by dissolving it in benzene and percolating through a column of alumina (Merck); crystallisation from hot ligroin (b. p. 60—80°) furnished *6-chloro-4-methylcinnoline* (3·6 g.) in almost colourless needles, m. p. 136—137° (Found: C, 60·0; H, 3·85; N, 16·4; Cl, 19·65. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·9; N, 15·7; Cl, 19·9%). The *picrate* (from alcohol) formed felted clusters of green needles, m. p. 154—156° (decomp.) (Found: N, 17·5. $C_{15}H_{10}O_7N_5Cl$ requires N, 17·2%).

Quaternary Salts of 4-Methylcinnolines.—The salts were readily formed when the cinnolines were refluxed in alcohol with excess of alkyl iodide for 2—3 hours, and were isolated without difficulty and in good yield by concentration of the solutions. *4-Methylcinnoline ethiodide* separated from alcohol–ether in fine red needles, m. p. 152—154° (Found: C, 43·8; H, 4·5. $C_{11}H_{13}N_2I$ requires C, 44·0; H, 4·4%). *6-Chloro-4-methylcinnoline ethiodide*, red prismatic needles from alcohol, had m. p. 204° (decomp.) (Found: C, 40·25; H, 3·9. $C_{11}H_{12}N_2ClI$ requires C, 39·5; H, 3·6%). *7-Chloro-4-methylcinnoline ethiodide* formed dark red needles, m. p. 185°, from alcohol–ether (Found: C, 39·45; H, 3·65%); the *methiodide*, red needles from methanol–ether, had m. p. 202° (decomp.) (Found: C, 37·2; H, 3·2. $C_{10}H_{10}N_2ClI$ requires C, 37·4; H, 3·15%). *4-Methyl-7-carbethoxycinnoline ethiodide*, m. p. 208° (decomp.), formed soft red needles from alcohol (Found: C, 45·3; H, 4·5. $C_{14}H_{17}O_2N_2I$ requires C, 45·15; H, 4·6%). Halogen estimations with these compounds were unsatisfactory.

4-p-Dimethylaminostyryl-1-ethylcinnolinium Iodides.—4-Methylcinnoline ethiodide (1 g.) was dissolved in warm acetic anhydride (16 c.c.) and *p*-dimethylaminobenzaldehyde (0·5 g.) added, and the deep blue solution refluxed gently (bath temp., 160°). Crystalline material separated after 10 minutes, and the amount did not visibly increase after 2 hours' refluxing. The crude product (0·23 g., m. p. 240—245°) was recrystallised from alcohol, *4-p-dimethylaminostyryl-1-ethylcinnolinium iodide* separating in needles, m. p. 252° (Found: C, 55·95; H, 5·1; N, 9·8. $C_{20}H_{23}N_3I$ requires C, 55·65; H, 5·15; N, 9·7%). Analogous styrylcinnolinium salts were also prepared by this method from the other ethiodides already described, but the condensations were more satisfactory when a 10% alcoholic solution of the ethiodide was refluxed for 2 hours with the theoretical amount of *p*-dimethylaminobenzaldehyde in the absence of catalyst, because, although the condensations were incomplete (unchanged aldehyde could be detected by smell), and the crude yields were about the same (*ca.* 30%) in each method, the products by using alcohol were much purer than those obtained by using acetic anhydride. *6-Chloro-4-p-dimethylaminostyryl-1-ethylcinnolinium iodide* formed needles, m. p. 248—250° (decomp.) from alcohol (Found: C, 50·1; H, 4·7; N, 8·0. $C_{20}H_{21}N_3ClI,\frac{1}{2}H_2O$ requires C, 50·6; H, 4·7; N, 8·85%). The *7-chloro*-isomer (needles from alcohol) had m. p. 246° (decomp.) (Found: C, 51·6; H, 4·8; N, 8·6. $C_{20}H_{21}N_3ClI$ requires C, 51·5; H, 4·55; N, 9·0%), and *7-carbethoxy-4-p-dimethylaminostyryl-1-ethylcinnolinium iodide*, after digestion with 50% aqueous alcohol to remove unchanged ethiodide, formed needles, m. p. 250° (decomp.) from alcohol (Found: C, 55·0; H, 5·35; N, 8·4. $C_{23}H_{25}O_2N_3I$ requires C, 54·9; H, 5·2; N, 8·35%). All these dyes exhibited a green reflex in the solid state, and gave deep blue solutions in alcohol; the colours were discharged by acid and by strong alkali.

Oxidation of 4-Methylcinnoline.—A solution of the base (1 g.) in water (20 c.c.) was treated at 28° with aqueous potassium permanganate (80 c.c.), added during 40 minutes with mechanical stirring. The initially rapid oxidation appeared to slow down considerably towards the end of the addition; a further 5 c.c. were added, and after a few minutes a little alcohol was added and the mixture filtered. Ether-extraction of the alkaline filtrate and washings gave a product from which 4-methylcinnoline [0·2 g., m. p. and mixed m. p. 74—75° (Found: C, 75·1; H, 5·65%); picrate, m. p. and mixed m. p. 179—180°] was recovered by digestion with ligroin (b. p. 60—80°). The alkaline solution, after concentration, gave no precipitate on acidification; addition of sodium acetate until the solution was no longer acid to Congo-red, followed by picric acid, gave a *picrate* (0·3 g.), which separated from hot water (charcoal) in long yellow needles, m. p. 342°, which tended to explode on analysis [Found: C, 27·3; H, 1·6; N, 15·8. $(C_6H_6O_{12}N_4)_x$ requires C, 27·4; H, 1·7; N, 16·0%].

We are indebted to Imperial Chemical Industries Limited (Dyestuffs Division) for their support of this investigation, and to the Council of the Durham Colleges for a grant from the Research Fund.

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[*Received, September 25th,* 1946.]

157. 3(β) : 6(β)-*Dihydroxycholanic Acid, an Epimeride of Hyodeoxycholic Acid.*

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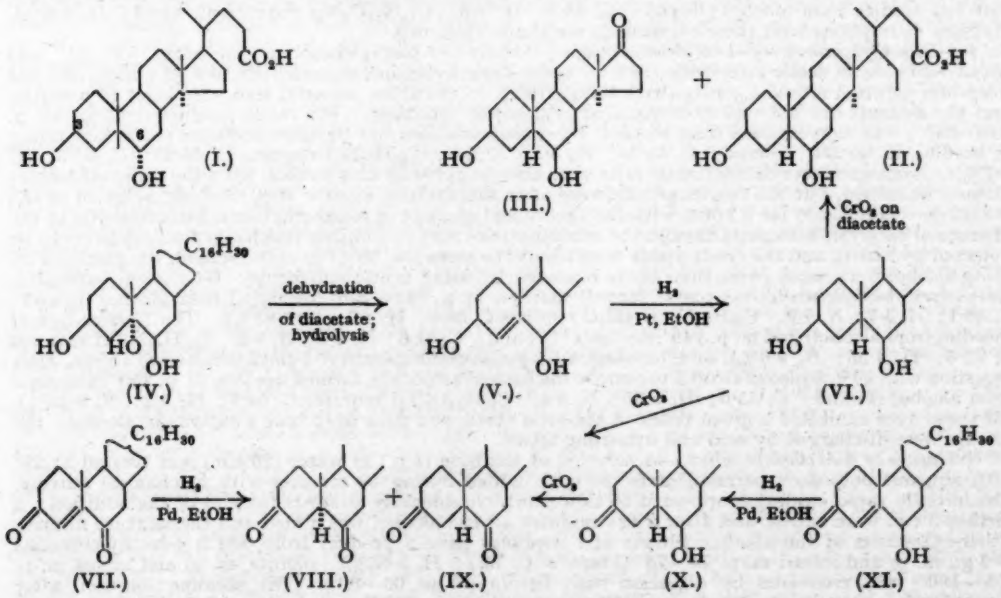
The oxidative degradation of coprostan-3(β) : 6(β)-diol (VI), by means of which 3(β) : 6(β)-dihydroxycholanic acid (II) and 3(β) : 6(β)-dihydroxyætiocholan-17-one (III) were obtained, is described. The acid (II) does not correspond in its properties to either of the known, naturally occuring 3 : 6-dihydroxycholanic acids, and hence "β"-hyodeoxycholic acid is 3(β) : 6(α)-dihydroxycholanic acid (I). Some preliminary experiments in connection with a possible route to coprostane-3(α) : 6(β)-diol from cholesterol are also described.

THE main structural features of "α"-hyodeoxycholic acid, isolated from pigs' bile, have been determined (Windaus and Bohne, *Annalen*, 1923, **433**, 278; Windaus, *ibid.*, 1926, **447**, 233; Wieland, Dane, and Martius, *Z. physiol. Chem.*, 1933, **215**, 18), and its formulation as a 3(α) : 6-dihydroxycholanic acid leaves only the configuration of the hydroxyl group at C_6 to be settled. Kimura (*ibid.*, 1937, **248**, 280) has reported the isolation, from the same natural source, of an epimeric 3 : 6-dihydroxycholanic acid ("β"-hyodeoxycholic acid) to which, by applying a series of degradation experiments analogous to those employed by Wieland *et al.* (*loc. cit.*) in the case of the "α"-isomer, he was able to assign the structure of a 3(β) : 6-dihydroxycholanic acid. The work now described is in continuation of a project to obtain 3 : 6-dihydroxycholanic acids from cholesterol in order to study the configurational relationships between "α"-hyodeoxycholic acid and its three theoretically possible epimerides (compare Paige, *J.*, 1943, 437), and shows that "β"-hyodeoxycholic acid is 3(β) : 6(α)-dihydroxycholanic acid (I).

The configuration assigned to the triol obtained by hydrogen peroxide oxidation of cholesterol (Pickard and Yates, *J.*, 1908, **93**, 1678) as cholestane-3(β) : 5 : 6(β)-triol (IV) (Ellis and Petrow, *J.*, 1939, 1078) has received further confirmation from the work of Plattner and Lang (*Helv. Chim. Acta*, 1944, **27**, 1872). Hydrogenation, with a platinum catalyst, of Δ^4-cholesten-3(β) : 6(β)-diol (V), obtained by hydrolysis of 3(β) : 6(β)-diacetoxy-Δ^4-cholestene, the product of



Darzens dehydration of the diacetate of (IV), was reported to give cholestane-3(β) : 6(β)-diol (Petrow, Rosenheim, and Starling, *J.*, 1938, 679). However, Prelog and Tagmann (*Helv. Chim. Acta*, 1944, **27**, 1880) have reinvestigated the hydrogenation and shown that the saturated diol (VI) obtained in good yield, by using an alcoholic medium, does in fact belong to the coprostane series, their evidence being based mainly on their observation that oxidation of the diol gave a saturated diketone (IX) which was isomeric with, but distinct from the known cholestane-3 : 6-dione (VIII), and was readily allomerised to the latter by dilute acid. In further support for the coprostane configuration of the saturated diol (VI), it is now found that catalytic hydrogenation of Δ^4-cholestene-3 : 6-dione (VII) in alcoholic solution with palladium (cf. Bretschneider, *Ber.*, 1941, **74**, 1361) gives a mixture from which are isolated cholestan-3 : 6-dione (VIII), in about 40% yield, and also about 20% of coprostane-3 : 6-dione (IX) identical with a specimen prepared according to Prelog and Tagmann.

3(β) : 6(β)-*Dihydroxycholanic acid* (II)* and 3(β) : 6(β)-*dihydroxyætiocholan*-17-*one* (III) were isolated from the products of oxidation of the diacetate of 3(β) : 6(β)-dihydroxycoprostane (VI). The dihydroxycholanic acid was characterised by oxidation to a diketo-acid (m. p. 161—162°),† which crystallised with one molecule of water from dilute ethanol, and further by isomerisation of this acid to the corresponding diketo-acid (m. p. 205°) of the C_5-*allo*-series. The identity of the last two acids with " α "-dehydrohyodeoxycholic acid monohydrate (m. p. 161·5—162°) and " β "-dehydrohyodeoxycholic acid (m. p. 209°), respectively, which were obtained from " α "-hyodeoxycholic acid (Windaus, *Annalen*, 1926, **447**, 233), appears certain. Since the properties of 3(β) : 6(β)-dihydroxycholanic acid (m. p. 250°) do not correspond to those of " β "-hyodeoxycholic acid (m. p. 189—190°), the latter acid must be 3(β) : 6(α)-dihydroxycholanic acid (I). It does not necessarily follow, however, that " α "-hyodeoxycholic acid has the configuration, 3(α) : 6(α)-dihydroxycholanic acid (compare Kimura, *loc. cit.*).

In order to examine the possibility of obtaining coprostane-3(α) : 6(β)-diol from cholesterol, catalytic hydrogenation of Δ^4-cholesten-6(β)-ol-3-one (XI), was studied. With a palladium catalyst, absorption of hydrogen ceased after about one molecule had been taken up, and the resulting gum gave in good yield, *coprostan*-6(β)-*ol*-3-*one semicarbazone*. The product obtained by hydrolysis of the semicarbazone was also a gum, but would appear to consist essentially of coprostan-6(β)-ol-3-one (X), since on oxidation it gave pure coprostane-3 : 6-dione (IX) in good yield. A possibly more convenient route to the saturated ketol (X) lies in partial hydrolysis of the diacetate of 3(β) : 6(β)-dihydroxycoprostane (VI) and subsequent oxidation. Hydrolysis yielded a crystalline hydroxyacetoxycoprostane which, by analogy with other partial hydrolyses of 3 : 6-diacetoxy-steroids previously reported in the literature (see, *e.g.*, Plattner and Lang, *loc. cit.*; Marker and Krueger, *J. Amer. Chem. Soc.*, 1940, **62**, 79), was presumed to be 6(β)-*acetoxycoprostan*-3(β)-*ol*. Circumstances have made it impracticable to complete further work which might be expected to lead to the projected transformation of this into 3(α) : 6(β)-dihydroxycholanic acid.

Experimental.

Hydrogenation of Δ^4-*Cholestene*-3 : 6-*dione* (VII).—A solution of the dione (1·0 g.) (Windaus, *Ber.*, 1906, **39**, 2249) in warm absolute ethanol (25 c.c.) was cooled quickly to room temperature, and the resulting suspension of small crystals shaken with palladium black (0·1 g.) in an atmosphere of hydrogen. Uptake reached a maximum (*ca.* 1·3 mols.) after 1 hour, and shaking was continued for a further hour. The mixture was warmed and filtered from catalyst, and the crystalline material which separated on cooling was combined with a further amount obtained by evaporation of the mother-liquors. Fractional

* *Added, May* 31*st*, 1947.—Since this paper was submitted for publication, it has been found that the same dihydroxycholanic acid was described in papers not hitherto accessible, and not abstracted in this country. Tukamoto (*J. Biochem. Japan*, 1941, **32**, 451, 467) obtained the four theoretically possible dihydroxycholanic acids by aluminium *iso*propoxide reduction of " α "-dehydrohyodeoxycholic acid prepared from natural " α "-hyodeoxycholic acid. Of these four stereoisomeric 3 : 6-dihydroxycholanic acids, the isomer, m. p. 258°, which gave 3(*β*)-hydroxy-6-ketocholanic acid, m. p. 189°, on partial oxidation (cf. Kimura, *Z. physiol. Chem.*, 1937, **248**, 280, who reported that the hydroxyketo-acid had m. p. 154°), was assigned the structure 3(*β*) : 6(*β*)-dihydroxycholanic acid, apparently arbitrarily in respect to the configuration of the hydroxyl group at C_3. The properties of 3(*β*) : 6(*β*)-dihydroxycholanic acid obtained by oxidation of the diacetate of coprostane-3(*β*) : 6(*β*)-diol, as described above, correspond to those of the dihydroxycholanic acid, m. p. 258°, described by Tukamoto. Further support for their identity has now been obtained by partial oxidation, with chromium trioxide, of the former acid under conditions similar to those employed by the Japanese author. The 3(*β*)-hydroxy-6-ketocholanic acid thus obtained formed prismatic needles from ether–pentane, m. p. 188° (Found : C, 74·2; H, 9·4. Calc. for $C_{24}H_{38}O_4$: C, 73·8; H, 9·7%). The author is indebted to Dr. R. B. Moffett who kindly presented micro-photostat copies of these Japanese publications.

† *Added, May* 31*st*, 1947.—The m. p. of the diketo-acid was not depressed by admixture with an authentic sample of " α "-dehydrohyodeoxycholic acid, prepared from natural " α "-hyodeoxycholic acid and supplied by Dr. R. B. Moffett.

crystallisation of the material yielded as less soluble product, needles (0·4 g.), m. p. 163—170°, $[\alpha]_D^{19°}$ + 10° (*c* = 0·902 in chloroform), of cholestane-3 : 6-dione which gave no depression in m. p. on admixture with an authentic sample (Windaus, *loc. cit.*), and as more soluble product, long needles (0·2 g.), m. p. 175—179°, $[\alpha]_D^{19°}$ − 82° (*c* = 0·268 in chloroform), of coprostane-3 : 6-dione. A sample of coprostane-3 : 6-dione prepared according to Prelog and Tagmann (*loc. cit.*) had m. p. 175—179°, $[\alpha]_D^{19°}$ − 79° (*c* = 0·33 in chloroform), and showed no depression in m. p. on admixture with the latter product.

Oxidation of the Diacetate of 3(β) : 6(β)-*Dihydroxycoprostane* (VI).—A mechanically stirred solution of the diacetoxy-compound (22·9 g.) (Prelog and Tagmann, *loc. cit.*) in glacial acetic acid (900 c.c.) was heated on the water-bath and treated dropwise during 6 hours with a solution of chromium trioxide (50 g.) in glacial acetic acid (150 c.c.) and water (28 c.c.). Heating was continued for a further 4 hours. After remaining overnight at room temperature, the mixture was treated with ethanol (25 c.c.), and then evaporated in a vacuum to small bulk. The residue was treated with 2N-sulphuric acid (750 c.c.) and extracted with ether, and the ethereal layer washed thrice with water and then extracted with 2N-sodium hydroxide (110 c.c.). The alkaline extract was saponified by heating on the water-bath for 2 hours. The sparingly soluble sodium salt thus obtained was separated (centrifuge), washed with a little water, dissolved in hot water, and the free acid precipitated by addition of concentrated hydrochloric acid. The crude material was filtered off and purified by extraction with boiling ethyl acetate (Soxhlet), followed by crystallisation from dilute ethanol, giving colourless plates (870 mg.), m. p. 250° of 3(β) : 6(β)-*dihydroxycholanic acid* (II) (Found : C, 73·4; H, 10·1. $C_{24}H_{40}O_4$ requires C, 73·5; H, 10· %). The ethereal solution from which acid substances had been removed was washed with water and evaporated. The residual oil was dissolved in warm methanol (45 c.c.), the solution allowed to cool, and seeded with a crystal of starting material. The unchanged diacetoxycoprostane which crystallised (1·6 g.) was filtered off, and the filtrate evaporated. The residue was freed from volatile, pleasant-smelling substances by distilling in steam. The residue was extracted with ether, the ethereal solution washed with water, and evaporated. The residual gum was dissolved in warm ethanol (30 c.c.), the solution treated with semicarbazide hydrochloride (0·85 g.), and sodium acetate (1·02 g.), and the mixture boiled under reflux on the water-bath for 2 hours. After cooling, ether and water were added. The ethereal layer was separated and washed repeatedly with small portions of water, until solid material started to separate. When separation was complete, the material was filtered off and washed with a little ether. Crystallisation from methanol gave microscopic, white needles (170 mg.), m. p. 218—220° (decomp.), of 3(β) : 6(β)-*diacetoxyætiocholan*-17-*one semicarbazone* (Found : C, 64·3; H, 8·0; N, 9·3. $C_{24}H_{37}O_5N_3$ requires C, 64·4; H, 8·3; N, 9·4%). This semicarbazone (149 mg.) was dissolved in warm ethanol (7·5 c.c.), the solution treated with a mixture of concentrated sulphuric acid (0·75 c.c.) and water (1·5 c.c.), and boiled under reflux for 30 minutes. After cooling, the mixture was treated with water and ether, and the ethereal layer washed with water and then evaporated. The residue was boiled under reflux with 2% methanolic potassium hydroxide (4·5 c.c.) for 1 hour. The solution was treated with water and extracted with ether. The ethereal layer was washed with water and then treated with pentane. Recrystallisation of the precipitate from ether–pentane gave colourless rhombs, m. p. 209—210°, of 3(β) : 6(β)-*dihydroxyætiocholan*-17-*one* (III) (Found : C, 74·8; H, 9·5. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%).

Oxidation of 3(β) : 6(β)-*Dihydroxycholanic Acid.*—A solution of the dihydroxy-acid (200 mg.) in warm acial acetic acid (7 c.c.) was cooled to room temperature and treated gradually, with shaking, with a solution of 80% acetic acid (3 c.c.) which contained chromium trioxide (128 mg.). After remaining at room temperature for 3½ hours, the solution was treated carefully with dilute sulphuric acid. The crystalline product was well washed with water and recrystallised from a small amount of glacial acetic acid. Further recrystallisation from dilute ethanol gave rectangular leaflets, m. p. 161—162°, of " α "-dehydrohyodeoxycholic acid monohydrate (Found : C, 71·2; H, 9·1. Calc. for $C_{24}H_{36}O_4.H_2O$: C, 70·9; H, 9·4%).

" β "-Dehydrohyodeoxycholic Acid.—The above diketo-acid (90 mg.) was boiled under reflux with glacial acetic acid (1·8 c.c.) containing one drop of concentrated hydrochloric acid for 1½ hours. The hot solution was carefully treated with water until it was faintly turbid, and the material which crystallised on cooling was repeatedly recrystallised from ethanol, giving minute, colourless leaflets, m. p. 205° (Found : C, 73·9; H, 9·4. Calc. for $C_{24}H_{36}O_4$: C, 74·2; H, 9·3%).

Hydrogenation of Δ⁴-*Cholesten*-6(β)-*ol*-3-*one* (XI).—A solution of the unsaturated hydroxy-ketone (400 mg.) (Ellis and Petrow, *J.*, 1939, 1081) in absolute ethanol (20 c.c.) was hydrogenated with palladium black (40 mg.) at room temperature. Absorption of hydrogen ceased after 20 minutes when approximately 1·1 mols. had been taken up. After filtration of catalyst, removal of the solvent in a vacuum left a hard, brittle gum which could not be obtained crystalline either by solvent treatment or by absorption from light petroleum (b. p. 60—80°) solution on a column of activated alumina followed by elution of the column with chloroform–methanol. The gum (330 mg.), dissolved in ethanol (10 c.c.), was treated with semicarbazide hydrochloride (137 mg.) and sodium acetate (167 mg.), and the mixture boiled under reflux on the water-bath for 2 hours; the solid material which had separated was filtered off and well washed with water. Crystallisation from ethanol gave minute leaflets (240 mg.), m. p. 202—203°, of *coprostan*-6(β)-*ol*-3-*one semicarbazone* (Found : C, 72·7; H, 10·2; N, 9·3. $C_{28}H_{49}O_2N_3$ requires C, 73·1; H, 10·7; N, 9·2%). Hydrolysis of this semicarbazone (147 mg.) with boiling 3N-aqueous-ethanolic sulphuric acid in the usual way regenerated a brittle gum. This (76 mg.) was dissolved in glacial acetic acid (4 c.c.), and the solution treated dropwise, with shaking, with 90% acetic acid (3·71 c.c.) containing chromium trioxide (23·6 mg.). After standing at room temperature for 15 hours, the solution was treated with a few drops of methanol, poured into water, and extracted with ether. The ethereal extract, after being washed with dilute sodium carbonate solution then with water and evaporated, left a crystalline residue which, on recrystallisation from methanol, gave long needles (60 mg.), m. p. 175—179°, $[\alpha]_D^{19°}$ − 76° (*c* = 0·332 in chloroform), of coprostane-3 : 6-dione, the m. p. of which was not depressed on admixture with an authentic sample.

6(β)-*Acetoxycoprostan*-3(β)-*ol.*—A solution of 3(β) : 6(β)-diacetoxycoprostane (488 mg.) in warm methanol (13·5 c.c.) was boiled under reflux on the water-bath, and the boiling solution treated dropwise,

during 30 minutes, with 0·189N-methanolic potassium hydroxide solution (5·56 c.c. = 1·05 mols.). Boiling was continued for a further 10 minutes, and the solution set aside for 12 hours. After acidification with a few drops of glacial acetic acid, the solution was evaporated to small bulk on the water-bath. The *substance* which separated was filtered off and triturated with water, giving a crystalline solid (300 mg.; m. p. 125—132°) which, after repeated recrystallisation from methanol, gave long, colourless leaflets, m. p. 143°, strongly depressed on admixture with starting material (Found: C, 78·2; H, 11·2. $C_{22}H_{30}O_3$ requires C, 78·0; H, 11·2%).

Grateful acknowledgment is made to Professor J. W. Cook, F.R.S., at whose instigation this work was begun, for his continued interest and stimulating advice, and to Mr. J. M. L. Cameron for micro-analyses.

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158. *A New Reaction of Thiocyanic Esters.*

By ERIC HOGGARTH and W. A. SEXTON.

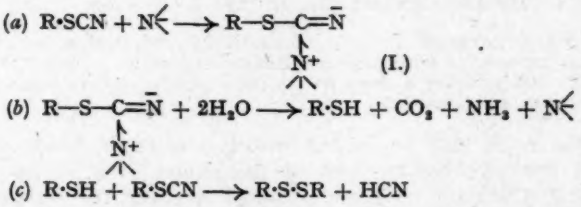
Thiocyanic esters are converted almost quantitatively into disulphides by heating with tertiary amines in acetic acid or with pyridine acetate in alcohol. This reaction also takes place with secondary and primary amines but is then complicated to some extent by side reactions. A mechanism is suggested.

REACTIONS of thiocyanic esters may be divided broadly into three classes, those in which the thiocyanate radical is severed from the rest of the molecule as in the rearrangement to *iso*thiocyanates, those in which the molecule is broken between the carbon and the sulphur atom as in reduction to thiols, and those in which there is addition to the cyanide part of the radical as, *e.g.*, in the cyclisation of *o*-aminophenyl thiocyanates to aminobenzthiazoles. A new reaction has been observed in which the initial step is thought to be of the third type, though followed by a scission of the adduct with elimination of the carbon and nitrogen atoms. When two molar proportions of a thiocyanic ester are heated with an acetic acid solution of one molar proportion of a tertiary amine, an almost quantitative conversion into disulphide takes place. The reaction has been carried out with *p*-nitrophenyl, *p*-chlorophenyl, *p*-tolyl, and benzyl thiocyanates using pyridine, dimethylaniline, and triethylamine as the amines, and it constitutes an attractive method for the preparation of pure disulphides. The reaction also takes place with secondary amines, *e.g.*, methylaniline, piperidine, and dibutylamine, and with primary amines such as anilines and *n*-butylamine, though the reaction is complicated by side reactions when some of these are used (see p. 817). The speed of the reaction is not influenced to any great extent by the amine used, but the thiocyanates vary in reactivity. Reaction is more rapid with *p*-nitrophenyl than with *p*-tolyl or *p*-chlorophenyl thiocyanates and a higher temperature must also be used in the latter cases. The reaction is slow also with benzyl thiocyanate and very slow with dodecyl thiocyanate. Challenger and Collins (*J.*, 1924, **125**, 1377) found that when *o*-nitrophenyl thiocyanate was boiled with aniline, a mixture of 2 : 2′-dinitrodiphenyl sulphide and the corresponding disulphide was formed. With the 2 : 4-dinitro-thiocyanate the main product was 2 : 4-dinitrodiphenylamine; some phenylthiourea and some 2 : 4 : 2′ : 4′-tetranitrodiphenyl sulphide were isolated and there was some evidence of a small amount of the corresponding disulphide. Although in these cases reaction conditions are very different from ours, disulphide formation may be the result of a reaction similar to that under consideration here.

The case of *p*-nitrophenyl thiocyanate and tertiary amines has been studied in detail and it has been found that the reaction takes place in a current of nitrogen. Since the disulphide crystallises out as the reaction proceeds, its formation cannot be due to aerial oxidation of the thiol. This distinguishes the reaction under discussion from the well-known conversion of thiocyanic esters into disulphides by hydrolysis with acids or alkalis, in which case access of air is necessary to oxidise thiol to disulphide (see, *e.g.*, Rabat, *Bull. Soc. chim.*, 1902, **27**, 690). During the reaction about one molecular proportion of both hydrogen cyanide and carbon dioxide are liberated and may be removed from the carrier gas by acid silver nitrate followed by baryta. No cyanogen was detected by the procedure of Wallis (*Annalen.*, 1906, **345**, 361). After dilution of the reaction mixture with water and separation of the disulphide, the aqueous liquor has been shown to contain about one molecular proportion of ammonia, and the tertiary base may be recovered unchanged. The reaction will not proceed at an appreciable speed with only a trace of tertiary base, and no reaction takes place even with the necessary proportion of base in a non-ionising solvent such as toluene. The reaction is normally carried out with free

access of atmospheric moisture and without taking precautions to dry the acetic acid. When care is taken to exclude water, however, no reaction takes place. Similarly, the reaction proceeds smoothly with pyridine acetate in ordinary methyl alcohol, but not if all materials are carefully dried.

To explain the foregoing observations the following mechanism is suggested: (*a*) A primary addition of tertiary base to the carbon atom of the thiocyanate group; this would be expected to be facilitated by electron-attracting groups in the radical R and explains the much more rapid reaction with *p*-nitrophenyl than with the other thiocyanates used. (*b*) Decomposition of the product (I) of stage (*a*) by water to give a thiol, carbon dioxide, and ammonia, with regeneration of the tertiary base; this may proceed through cyanic acid as an intermediate step (compare the formation of cyanate by alkaline treatment of 1-thiocyanobenzthiazole; Davies and Sexton, *J.*, 1944, 11). (*c*) Reaction of the thiol with the remaing thiocyanate to give disulphide and hydrogen cyanide. The final stage has been shown to proceed very readily when an acetic acid solution of equimolecular quantities of a thiocyanate and a thiol is heated.



(*a*) $R{\cdot}SCN + N\langle \longrightarrow R{-}S{-}C{=}\bar{N}$ with $N^+\langle$ (I.)

(*b*) $R{-}S{-}C{=}\bar{N} + 2H_2O \longrightarrow R{\cdot}SH + CO_2 + NH_3 + N\langle$ with $N^+\langle$

(*c*) $R{\cdot}SH + R{\cdot}SCN \longrightarrow R{\cdot}S{\cdot}SR + HCN$

With secondary amines such as methylaniline the base is recovered after reaction as the acetyl derivative. A small amount of an unidentified by-product has been isolated also, after alkaline hydrolysis of the separated acetamido-compound. Using aniline, much *s*-diphenylguanidine is formed as well as acetanilide, and this may be ascribed to attack of the postulated intermediate compound (I) by a second molecule of aniline. These side reactions are reflected in the smaller amounts of ammonia and carbon dioxide which are obtained in the reactions with methylaniline and especially aniline. The reaction will also take place (though very much more slowly) with ammonia in the case of *p*-nitrophenyl thiocyanate. It is possible that a certain amount of disulphide is produced in the reactions with amines by the ammonia liberated in stage (*b*) of the postulated mechanism, though in view of the very slow speed of the reaction with ammonia alone, this is not likely to account for any considerable proportion of the product.

The nature of the reagent used to bring about fission of the thiocyanate in this way is such as to suggest that the reaction might proceed under physiological conditions. If this is so, then the reaction described may be associated with the biological activity of the thiocyanates, which covers toxicity to fungi, insects, and higher animals depending on the group attached to SCN.

Experimental.

Reaction of p-*Nitrophenyl Thiocyanate with Various Amines.*—*p*-Nitrophenyl thiocyanate (18 g.), acetic acid (25 c.c.), and an amine (0·05 g.-mol.) were heated for 18 hrs. at 100° (bath temp.). Large yellow prisms, m. p. 180—182°, gradually formed and after a further 6 hrs.' standing, were collected and washed with a little acetic acid. The m. p. was not raised appreciably by crystallisation from 2-ethoxyethanol but this was desirable in some cases (especially with dimethylaniline) to remove a trace of coloured impurity. The following amines were used, with the yields given: pyridine 14·7 g., dimethylaniline 14·4 g., triethylamine 14·2 g., methylaniline 14·5 g., dibutylamine 14·0 g., piperidine 14·2 g., aniline 14·8 g., *p*-toluidine 14·4 g., *n*-butylamine 14·8 g.

Reaction of Various Thiocyanates with Pyridine.—The thiocyanate (0·0333 g.-mol.) in acetic acid (7·5 c.c.) and pyridine (1·3 g.) was heated for 50 hrs. at 130—135° (bath temp.). Water and ice (about 100 c.c.) were added, and the oil allowed to solidify, collected, washed with water, and dried in a vacuum. The following disulphides were prepared and identified by mixed m. p. determinations with authentic samples: 4 : 4′-dichlorodiphenyl (4·5 g.), m. p. 72—74°; 4 : 4′-ditolyl (3·8 g.), m. p. 45—46°; dibenzyl (3·4 g.), m. p. 71°. With dodecyl thiocyanate (7·6 g.), only partial conversion was obtained. By distillation of the product, unchanged thiocyanate (3·5 g.), b. p. 148—150°/1·0 mm., and didodecyl disulphide (3·2 g.), b. p. 228—230°/1·0 mm., m. p. 33°, were obtained.

Reaction of p-*Nitrophenyl Thiocyanate with Pyridine.*—A mixture of the thiocyanate (6·0 g., 0·0333 g.-mol.), pyridine (1·3 g., 0·0167 g.-mol.), and acetic acid (7·5 c.c.) was heated at 90—95° (bath temp.) in a slow stream of nitrogen (freed from traces of carbon dioxide by passage through dilute sodium hydroxide solution). The effluent gases were washed in three bubblers containing silver nitrate (10 g.) and concentrated nitric acid (15 c.c.) in distilled water (60 c.c.), and then in three more bubblers containing saturated baryta solution. (The last bubbler of each set remained clear, showing that absorption was complete.) Evolution of hydrogen cyanide and carbon dioxide began as soon as the internal temperature reached 80—85°, and was rapid for 4—5 hrs. By a suitable arrangement of taps,

the gas stream was diverted through fresh solutions of silver nitrate and baryta from time to time, and it was found that liberation of these gases ceased after 7—8 hrs. After 12 hrs.' heating in all, the reaction liquid was allowed to cool, and the 4 : 4'-dinitrodiphenyl disulphide (4·7 g., 0·0152 g.-mol.; m. p. 182—183°) was collected, washed with a little acetic acid, and dried. The filtrate was placed in a Kjeldahl apparatus, treated with saturated potassium hydroxide solution (50 c.c.), and steam-distilled into N-hydrochloric acid (50 c.c.). The back titration (34·5 c.c.) corresponded to 0·0155 g.-mol. of ammonia. The titration liquor was made strongly acid (hydrochloric acid), evaporated under reduced pressure, and the residue treated with saturated potassium hydroxide solution (20 c.c.) (ammonia was plainly recognised by smell). The liberated oil was extracted with ether, dried over sodium hydroxide, and distilled, giving a colourless oil (0·75 g.), b. p. 105—115°. [A better recovery of pyridine was obtained in a second experiment by evaporating the dried ethereal extracts to 10 c.c. and pouring them into a solution of picric acid in alcohol. The picrate was crystallised from aqueous 2-ethoxyethanol, giving yellow needles (3·9 g. = 1·0 g. of base), m. p. 167°.] The silver cyanide (1·85 g., 0·0137 g.-mol.) and barium carbonate (2·8 g., 0·0142 g.-mol.) were washed with hot distilled water and dried to constant weight at 110°. The silver cyanide was identified by evolution of cyanogen on heating (Found : Ag, 80·7. Calc. for AgCN : Ag, 80·6%). In the second experiment referred to above, the effluent gases were absorbed in ammonia solution which was then slowly evaporated in an open dish. The very small residue (ammonium acetate ?) was free from urea, for, when dissolved in a little 50% acetic acid, it gave no precipitate with a solution of xanthhydrol in alcohol. According to Wallis (*loc. cit.*) this proves the absence of cyanogen in the washed gases.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide in Presence of a Trace (only) of Pyridine.*—*p*-Nitrophenyl thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and pyridine (0·1 g.) were heated on the steam-bath for 36 hrs. There was no crystallisation of disulphide during this time. Water (100 c.c.) was added, and the solid collected, and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (5·1 g.), m. p. 128—129°. The result was exactly similar when dimethylaniline (0·1 g.) was used in place of the pyridine.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide in Toluene.*—The thiocyanate (6·0 g.), pyridine (1·4 g.), and toluene (35 c.c.) were refluxed for 24 hrs. The solvent was evaporated to 10 c.c., light petroleum (50 c.c.) added, and the solid collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (4·7 g.), m. p. 130°.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide with Exclusion of Water.*—A mixture of acetic acid (15 c.c.), acetic anhydride (5 c.c.), and pyridine (1·4 g.) was refluxed under a calcium chloride tube for 5 hrs., *p*-nitrophenyl thiocyanate (6·0 g.) was added, and heating at 95—100° continued for 36 hrs. No disulphide separated, and the reaction liquid was poured into ice and water (200 c.c.), and the solid collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (2·5 g.), m. p. 128—130°. The result was similar when dry dimethylaniline (2·0 g.) was added along with the thiocyanate to the dried acetic acid.

Reaction of p-*Nitrophenyl Thiocyanate with Pyridine Acetate in Methyl Alcohol.*—A mixture of the thiocyanate (6·0 g.), acetic acid (1 g.), pyridine (1·4 g.), and methyl alcohol (50 c.c.) was heated on the steam-bath under reflux for 18 hrs. After cooling, the solid was collected (4·1 g.), m. p. 182° not depressed by 4 : 4'-dinitrodiphenyl disulphide. The experiment was repeated, but each compound was dried carefully beforehand, and the mixture protected from atmospheric moisture. After cooling, the solid was collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (5·2 g.), m. p. 131°.

Reaction of p-*Chlorophenyl Thiocyanate with Dimethylaniline.*—The thiocyanate (5·7 g., 0·0333 g.-mol.), acetic acid (7·5 c.c.), and dimethylaniline (2·0 g., 0·0167 g.-mol.) were heated at 130—135° in the apparatus described on p. 816. Evolution of gases took place during 18 hrs., and heating was continued for 20 hrs. in all. Water (50 c.c.) was added to the reaction liquid, and the disulphide (4·5 g., m. p. 73—74°) collected and dried in a vacuum. The filtrate was distilled with alkali into N-hydrochloric acid and found to contain 0·0132 g.-mol. of ammonia. The titration liquid was extracted with ether, and the dimethylaniline dried over sodium sulphide and distilled, giving a colourless oil (1·1 g.), b. p. 190—194°/760 mm. Silver cyanide (2·0 g., 0·0149 g.-mol.) (Found : Ag, 80·9%) and barium carbonate (2·95 g., 0·0150 g.-mol.) were obtained as previously.

Reaction between p-*Chlorophenyl Thiocyanate and* p-*Chlorothiophenol.*—A mixture of *p*-chlorothiophenol (2·4 g.) and *p*-chlorophenyl thiocyanate (2·8 g.) was heated in acetic acid at 100° in a slow stream of nitrogen, until evolution of hydrogen cyanide ceased (8 hrs.). During this time silver cyanide (2·6 g.) collected, and on dilution of the reaction liquid with ice and water, 4 : 4'-dichlorodiphenyl disulphide (4·3 g.), m. p. 73—74°, was obtained.

Reaction of p-*Nitrophenyl Thiocyanate with Methylaniline.*—A mixture of the thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and methylaniline (3·6 g.) was heated for 12 hrs. at 95—100° and gave 4 : 4'-dinitrodiphenyl disulphide (4·8 g.), m. p. 182—183°, and ammonia corresponding to only 0·0101 g.-mol. The amount of barium carbonate (1·95 g., 0·0099 g.-mol.) was also less than in the preceding experiments although the amount of silver cyanide (1·8 g., 0·0134 g.-mol.) was normal. The oil extracted by ether from the titration liquid was distilled, giving methylaniline (1·8 g.), b. p. 194—198°/760 mm., and a higher fraction, b. p. 200—235°/760 mm. (1·0 g.), setting to a crystalline solid. From light petroleum (b. p. 60—80°) the latter crystallised in colourless plates (0·55 g.), m. p. 101°, not depressed by acetmethylanilide. Apparently the base is acetylated in the reaction and only partly hydrolysed in the Kjeldahl apparatus. In a repeat experiment on three times the above scale, the oil extracted from the steam-distillate was hydrolysed by refluxing for 12 hrs. with sodium hydroxide solution, and on distillation gave methylaniline (6·8 g.) and a very small high fraction, b. p. 220—230° (0·8 g.). The latter compound (m. p. 50—52°, depressed by acetmethylanilide) has not been further investigated.

Reaction of p-*Nitrophenyl Thiocyanate with Aniline.*—A mixture of the thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and aniline (3·1 g.) after being heated for 12 hrs. at 95—100° gave the disulphide (5·0 g., m. p. 180°) and ammonia corresponding to only 0·0062 g.-mol. The amount of barium carbonate (1·1 g., 0·0056 g.-mol.) was also much less than usual though the weight of silver cyanide was normal (2·05 g.,

0·0153 g.-mol.). The residual liquor in the Kjeldahl apparatus was cooled, and the solid collected and crystallised from benzene–light petroleum, giving *s*-diphenylguanidine (0·9 g.), m. p. 150° (no depression with authentic material). In a repeat experiment on six times the above scale, the acetic acid filtrate after separation of the disulphide was evaporated to dryness, the residue warmed with concentrated hydrochloric acid (50 c.c.) and water (250 c.c.), filtered (charcoal), and allowed to crystallise; colourless leaflets of acetanilide (12·0 g.), m. p. 100—104°, separated. The filtrate was made strongly alkaline with sodium hydroxide solution, and the precipitated solid crystallised from benzene–light petroleum (b. p. 60—80°), giving colouless plates (5·6 g.), m. p. 148°, not depressed by *s*-diphenylguanidine (Found: C, 74·0; H, 6·5; N, 19·6. Calc. for $C_{13}H_{12}N_2$: C, 73·9; H, 6·2; N, 19·9%).

Reaction of p-*Nitrophenyl Thiocyanate with Ammonia.*—The thiocyanate (6·0 g.), ammonium acetate (2·6 g., 0·0333 g.-mol.), and acetic acid (7·5 c.c.) were heated for 50 hrs. at 100—105°. Crystals slowly formed, and after standing for 6 hrs. they were collected and washed with a little acetic acid, giving the disulphide (4·9 g.), m. p. 182—183°. The filtrate contained 0·0421 g.-mol. of ammonia.

We are indebted to Professor A. R. Todd, F.R.S., for helpful suggestions which led us to the elucidation of the mechanism of the reaction described.

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159. *Oxidation of* [2 : 2 : 1]bicyclo*Heptene*-2 (*Norbornylene*).

By S. F. BIRCH, W. J. OLDHAM, and E. A. JOHNSON.

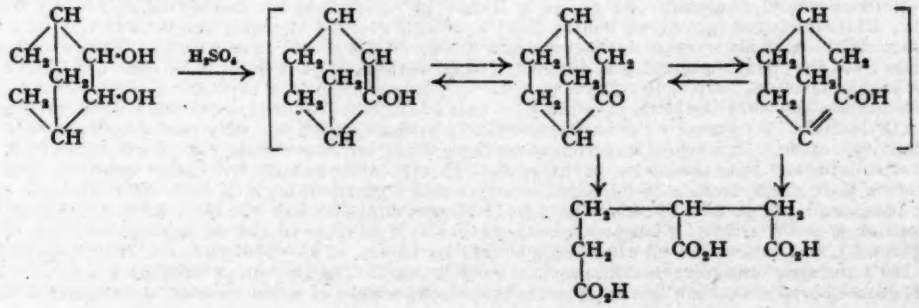
The preparation of *cyclo*pentane-*cis*-1 : 3-dicarboxylic acid is readily effected by oxidation of norbornylene with aqueous sodium permanganate, the pH of the reaction being controlled by the continuous passage of carbon dioxide through the reaction mixture during the permanganate addition. This method of oxidation may be applicable to other olefins and unsaturated compounds. The end-point of the reaction appears to be very sharp, and it is even possible that certain unsaturated compounds could be determined in this way.

The oxidation of norbornylene in glacial acetic acid solution with hydrogen peroxide yields a glycol, but further oxidation of this with chromic acid gives, not *cyclo*pentanedicarboxylic acid, but butane-1 : 2 : 4-tricarboxylic acid, indicating that some rearrangement occurs. This reaction was, however, not further investigated.

IN the course of work on the synthesis of substituted *cyclo*pentanes, it became desirable to prepare *cyclo*pentane-*cis*-1 : 3-dicarboxylic acid in a quantity of several kilograms. The method of preparation used by Pospischill (*Ber.*, 1898, **31**, 1950) and later by Perkin and Scarborough (*J.*, 1921, **119**, 1405) was briefly investigated but was so obviously unsuitable for the production of appreciable quantities of the acid that search was made for a simpler alternative.

The straightforward oxidation of [2 : 2 : 1]*bicyclo*heptene-2 (norbornylene) should yield the desired acid, since the carbon atoms in the unsaturated bridge must lie in a *cis*-position in relation to the remaining *cyclo*pentane ring. Norbornylene can be readily prepared in quantity by condensing *cyclo*pentadiene with ethylene according to the method of Joshel and Butz (*J. Amer. Chem. Soc.*, 1941, **63**, 3350).

Oxidation of norbornylene in glacial acetic acid with 30% hydrogen peroxide in the normal way was found to give a mixture of the *glycol* and its monoacetate. Further, oxidation of this mixture with chromic–sulphuric acid (Bennett and Gudgeon, *J.*, 1938, 1679) gave a mixture of acids which, when esterified and fractionated under reduced pressure, contained no detectable quantity of the required ester. The main component was identified as butane-1 : 2 : 4-tricarboxylic acid by conversion into *cyclo*pentanone-3-carboxylic acid according to the method given by Kay and Perkin (*J.*, 1906, **89**, 1643) and Haworth and Perkin (*J.*, 1908, **93**, 575). Some rearrangement must, therefore, have taken place, probably by the action of the sulphuric acid present on the glycol:



The above scheme is merely a suggested method of rearrangement. No investigation of the mechanism of the reaction was carried out.

Direct oxidation of norbornylene in *iso*octane solution with potassium permanganate, however, gave the required acid in low yield. The volume of solution to be worked up at the end of the oxidation was considerable owing to the relatively low solubility of potassium permanganate, and it was obvious that, unless the method could be improved, the preparation of the required acid in quantity would be extremely tedious and time-consuming. Further, the yield varied considerably in repeat experiments carried out under apparently identical conditions.

Search was therefore made for a method in which the reaction conditions could be more accurately controlled. Control of the temperature and of the pH of the reactants appeared to be possible methods of directing the course of the oxidation and improving the yield of the required acid. The use of the more soluble sodium permanganate in place of the potassium salt should minimise the volume of solution to be handled at the end of the experiment.

An experiment was therefore carried out in which norbornylene was oxidised in *iso*octane solution with aqueous sodium permanganate at 5—10°. It was found that the colour of permanganate persisted after the addition of approximately the theoretical amount. This had not been observed in any of the previous work. The crude acid was semi-solid and was much cleaner than that obtained previously. The yield was 65%.

Eventually, it was found that an excellent yield of clean product could be obtained by carrying out the oxidation with sodium permanganate and controlling the pH of the reaction mixture by passing a stream of carbon dioxide through it during the permanganate addition. Control of the temperature to 5—10° was found to be unnecessary, but it was not allowed to rise above 50°. The end of the reaction was indicated by the presence of excess permanganate in the mixture. The crude acid was pale yellow, immediately crystallisable, and was consistently obtained in good yield (95%).

Experimental.

(a) *Oxidation of Norbornylene with Hydrogen Peroxide and Chromic Acid.*—Norbornylene (47 g.) was dissolved in glacial acetic acid (1000 ml.), and hydrogen peroxide (100-vol., 268 ml.) added with stirring. A slight reprecipitation of norbornylene occurred, but this redissolved on standing for 48 hours at room temperature. The product was steam-distilled to remove most of the acetic acid, and concentrated under reduced pressure to about 300 ml. Sodium bicarbonate was then added until no further effervescence occurred, and the solution was extracted continuously with ether. The product distilled between 140° and 150°/19 mm., and the higher-boiling portion tended to crystallise. Some of this solid was separated and recrystallised, first from benzene–light petroleum, then twice from di*iso*propyl ether. It then melted at 185—185·5° (corr.) with some decomposition.

Analysis of the liquid portion of the distillate indicated that it might be a mixture of the glycol and its monoacetate. A portion was refluxed with potassium hydroxide solution and the solid glycol was extracted from the dark product with carbon tetrachloride. The solid was therefore probably 2 : 3-*dihydroxy*-[2 : 2 : 1]bicyclo*heptane* (trans-?) (Found : C, 65·8; H, 9·6. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). This product was not isolated in normal runs, but was oxidised further with chromic acid. The crude mixed acids were extracted continuously and converted into the ethyl esters.

From 330 g. of norbornylene, 284 g. of mixed esters were obtained. These were then fractionated under reduced pressure in a small column of about 40 theoretical plates, and were found to contain 173 g. of a product which boiled steadily at 162°/6 mm. The only other component identified was ethyl succinate; there was no detectable quantity of *cyclo*pentanedicarboxylic ester.

The acid obtained from the high-boiling ester could be crystallised from acetone–light petroleum, and after two such crystallisations melted at 119·3—119·9° (corr.) after thorough drying in a vacuum oven [Found : C, 44·5; H, 5·3; equiv., by titration with baryta, 63·0. Calc. for $C_4H_7(CO_2H)_2$: C, 44·2; H, 5·3%; equiv., 63·4]. The triethyl ester had b. p. 162°/6 mm., $n_D^{25°}$ 1·4390, $d_4^{25°}$ 1·0755 [Found : C, 57·1; H, 8·1; *M* (micro-Rast), 268. Calc. for $C_{13}H_{22}O_6$: C, 56·9; H, 8·1%; *M*, 274·4]. 13·7 G. of the ester were subjected to the Dieckmann condensation as described by Kay and Perkin (*loc. cit.*) (see also Haworth and Perkin, *loc. cit.*), and ethyl *cyclo*pentanone-2 : 3-dicarboxylate (6·5 g.) was obtained, b. p. 108°/0·9 mm., $n_D^{20°}$ 1·4574; it gave an intense crimson colour with ferric chloride (Found : C, 58·3; H, 7·4. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·1%).

Acid hydrolysis of this ester (5 g.) gave *cyclo*pentanone-3-carboxylic acid (2·5 g.) which, after two crystallisations from di*iso*propyl ether, melted at 61·0—62·0° (corr.) (Found : C, 56·4; H, 6·3. Calc. for $C_6H_8O_3$: C, 56·2; H, 6·3%).

The oxime was prepared, but decomposed above 160° with charring but without melting.

(b) *Oxidation of Norbornylene to* cis-cyclo*Pentane*-1 : 3-*dicarboxylic Acid.*—Norbornylene (100 g.) was dissolved in *iso*octane (200 ml.), and the solution was added to 3 l. of water in a 10-l. flask fitted with a tap-funnel, thermometer, bell stirrer, and carbon dioxide inlet tube. A steady stream of carbon dioxide was passed in while a 15% solution of sodium permanganate was added with vigorous stirring at such a rate that the temperature did not rise above 50°. When the reaction was complete the colour of permanganate persisted even on prolonged stirring. About 3480 g. of the permanganate solution were required, and the addition took about 4 hours. Sulphur dioxide was then passed in to remove manganese dioxide, and the *iso*octane was recovered for re-use by steam distillation. The clear, pale pink solution was concentrated to about 2 l., acidified with sulphuric acid (500 g.) in water (700 g.), and extracted with

three portions of ether (3 × 500 ml.). On removal of ether from the combined extract, 130 g. of pale yellow acid remained, m. p. 109—111°.

Continuous extraction of the remaining aqueous solution with ether yielded a further 25—30 g. of acid; this was often dark, owing possibly to further oxidation by traces of nitrate present in the permanganate, since red fumes were sometimes observed. After one recrystallisation from benzene, 115 g. of acid, m. p. 116°, were obtained; the chief impurity was probably the anhydride, since the benzene solution was refluxed for 2 hours in an apparatus for the removal of water, which continued to be formed in small quantity. A further recrystallisation from water, in which the acid is very soluble, raised the m. p. to 119·9—120·6° (corr.), unaffected by repeated recrystallisations from water (Found : C, 53·6; H, 6·7. Calc. for $C_7H_{10}O_4$: C, 53·2; H, 6·4%). The ethyl ester had b. p. 146°/20 mm., $n_D^{20°}$ 1·4474, $d_4^{20°}$ 1·0574 (Found : C, 61·7; H, 8·4. Calc. for $C_{11}H_{18}O_4$: C, 61·7; H, 8·5%).

We wish to record our thanks to the Chairman of the Anglo-Iranian Oil Company, Limited, for permission to publish this work.

ANGLO-IRANIAN OIL CO., LTD.,
RESEARCH STATION, SUNBURY-ON-THAMES, MIDDLESEX. [*Received, October 7th*, 1946.]

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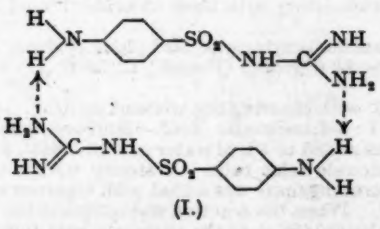
160. *Derivatives of Sulphanilylguanidine : Preparation for Pharmacological Study.*

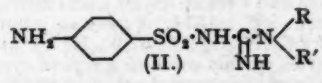
By E. HAWORTH, F. L. ROSE and F. H. SLINGER.

Mono- and di-alkyl derivatives of sulphanilylguanidine, prepared by a modification of the method of Birtwell *et al.* (*J.*, 1946, 491), together with *m*-aminobenzenesulphonylguanidine and β-sulphanilyl-α-acetylguanidine, are described. These substances were required in connection with a hypothesis relating to the pharmacological properties of the sulphanilylguanidine class of drug.

p-AMINOBENZENESULPHONYLGUANIDINE (sulphanilylguanidine, sulphaguanidine) is of value for the treatment of certain pathogenic intestinal infections. It was introduced for this purpose following the observation that, when given by mouth to animals, only a small percentage (20—40) was absorbed from the gut (Roblin *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 2002; Marshall *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163; 1944, **68**, 94). Sulphanilylguanidine is rather less soluble in water than sulphanilamide, but many times more soluble than drugs such as " sulphadiazine " and " sulphapyridine " which are well absorbed, so that this factor seems unimportant in determining pharmacological behaviour. Hitherto, no explanation of the peculiar influence of the guanidine group has been attempted, but recently it has been tentatively suggested by one of us (F. L. R.) that a physical association of sulphaguanidine through hydrogen-bonding either with some component of the gut wall or content or with itself to give a dimeric molecule of type (I) might be an important factor. The work of Hunter (*J.*, 1941, 777) has drawn attention to an intermolecular association through hydrogen bonds of amidino- and guanidino-groups, although in a different manner from the special case proposed in (I). Without discussing the theoretical merits of such an arrangement or the precise manner in which it might operate to inhibit passage through the gut wall, it was apparent that such changes in the molecule as the transfer of the primary amino-group to the meta position, or its replacement by nitro-, or the attachment of alkyl groups to the several nitrogen atoms, would depress or enhance the stability of any such association, and this should be reflected in greater or lesser absorption from the gastro-intestinal tract. The experimental determination of these effects and a discussion of the results obtained will be reported elsewhere (Rose and Spinks, *Brit. J. Pharm. Chemotherapy*, in the press); we record here the preparation of the new substances used in this



(I.)



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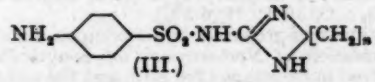

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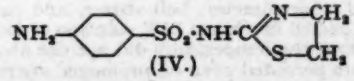
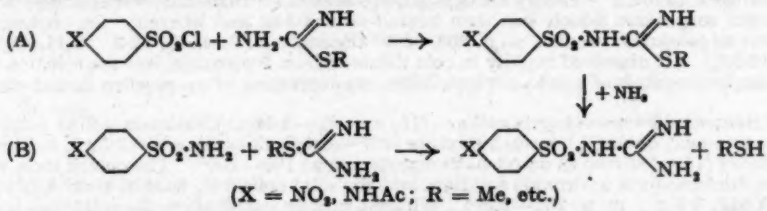


(IV.)

investigation together with several related compounds, which are novel either in themselves or in their preparative route. They are the monosubstituted derivatives (II; R = H, R′ = Me,

C_2H_4·OMe, C_2H_4·NEt_2, Ac), the disubstituted derivatives (II; R = R′ = Me, Et), the cyclic compounds (III, n = 2, 3) and (IV), and the meta-isomer of sulphaguanidine.

Winnek *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1682) have described the preparation of compounds of type (II) (R = H; R′ = Et, Pr, Bu) by the interaction of an *N*-sulphonylcyanamide with the appropriate alkylamine. Birtwell *et al.* (*J.*, 1946, 491) recorded the formation of sulphanilylguanidine by a number of routes including the following:



(X = NO_2, NHAc; R = Me, etc.)

With two exceptions, the substances described herein were made by a modification of (A) or (B), ammonia being replaced by a primary or secondary amine, and *iso*thiourea by an *N*-substituted *iso*thiourea. The para-substituent X was — NHAc in every instance save one, and the final reaction involving the synthesis of the guanidine residue was carried out mainly in phenol as solvent; in reaction (B) the appropriate *iso*thiourea was used in the form of its sulphate, and the sulphonamide as its sodio-derivative. The meta-isomer of sulphanilylguanidine was made by a route analogous to that employed by Roblin *et al.* (*loc. cit.*), namely the reduction of the condensation product of *m*-nitrobenzenesulphonyl chloride and guanidine. Compound (II, R = H, R′ = Ac) was obtained by reducing the reaction product of *p*-nitrobenzenesulphonylguanidine and acetic anhydride. The attachment of the acetyl residue to the terminal nitrogen atom was assumed.

The antibacterial activity of these substances against *Streptococcus pyogenes in vitro* has been examined by our colleague Dr. A. R. Martin. All were less effective than sulphanilylguanidine. The meta-isomer of sulphanilylguanidine, as anticipated, and the compound (II, R = H, R′ = C_2H_4·NEt_2), were devoid of antibacterial activity. Relatively high blood concentrations were achieved in mice following oral administration of *p*-nitrobenzenesulphonylguanidine, the meta-isomer of sulphanilylguanidine, and compound (II) in which R and R′ were both alkyl groups.

Experimental.

(Melting points are uncorrected.)

β-Sulphanilyl-α-methylguanidine (II, R = H, R′ = Me).—*p*-Acetamidobenzenesulphonyl-*S*-methyl-*iso*thiourea (27 g., Birtwell *et al.*, *loc. cit.*) was added to a stirred melt of phenol (48 g.) heated in an oil-bath maintained at 110°. Dry methylamine was passed into the mixture until the effluent gases gave no marked stain on lead acetate paper. The melt was added to sodium hydroxide (20 g.) in ice–water (250 c.c.), and the crystals which separated were filtered off, washed alkali-free with water, and dried at 100°. The crude product (12 g.) gave *β*-p-*acetamidobenzenesulphonyl-α-methylguanidine* (6 g.) in colourless rhombic prisms from water, m. p. 248—249° (Found: C, 44·65; H, 5·0; N, 20·0. $C_{10}H_{14}O_3N_4S$ requires C, 44·4; H, 5·2; N, 20·8%). The acetyl derivative (12·6 g.) was refluxed with N-hydrochloric acid (110 c.c.) for ½ hour. The resultant solution was made just alkaline with sodium hydroxide solution while still hot. On cooling, *β-sulphanilyl-α-methylguanidine* (7·4 g.) crystallised; after recrystallisation from water it had m. p. 163—165° (Found: C, 42·0; H, 5·25; N, 24·2. $C_8H_{12}O_2N_4S$ requires C, 42·2; H, 5·3; N, 24·6%).

β-Sulphanilyl-αα-dimethylguanidine (II, R = R′ = Me).—This *compound*, similarly prepared using dimethylamine, formed colourless rhombic plates, m. p. 164—165° (Found: C, 44·8; H, 5·7; N, 22·8. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8; N, 23·2%). The intermediate *acetamido*-derivative had m. p. 263—265° (Found: C, 46·25; H, 6·1; N, 19·4. $C_{11}H_{16}O_3N_4S$ requires C, 46·1; H, 5·7; N, 19·8%).

β-Sulphanilyl-αα-diethylguanidine (II, R = R′ = Et).—This *compound*, similarly prepared using diethylamine, formed slender colourless prisms, m. p. 141—142° (Found: C, 44·75; H, 6·5; N, 20·05. $C_{11}H_{18}O_2N_4S$ requires C, 44·8; H, 6·7; N, 20·8%). The intermediate *acetamido*-derivative formed colourless plates from water, m. p. 177—178° (Found: N, 18·05. $C_{13}H_{20}O_3N_4S$ requires N, 18·0%).

β-Sulphanilyl-α-2-methoxyethylguanidine (II, R = H, R′ = C_2H_4·OMe).—The use of phenol as a solvent was dispensed with. *p*-Acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea (5 g.) and 2-methoxyethylamine (10 g.) were stirred under reflux for 3 hours. The melt added to water gave crude *β*-p-*acetamidobenzenesulphonyl-α-2-methoxyethylguanidine* (3 g.) which when recrystallised from water had m. p. 178—180° (Found: C, 46·3; H, 5·9; N, 17·8. $C_{12}H_{18}O_4N_4S$ requires C, 45·8; H, 5·7; N, 17·8%). Hydrolysis at the acetamido-group effected as above gave *β-sulphanilyl-α-2-methoxyethylguanidine* as colourless prisms from water, m. p. 161—162° (Found: C, 44·25; H, 5·45; N, 19·95. $C_{10}H_{16}O_3N_4S$ requires C, 43·8; H, 5·1; N, 20·5%).

β-Sulphanilyl-α-2-diethylaminoethylguanidine (II, R = H, R′ = C_2H_4·NEt_2).—Prepared as for the methoxyethyl derivative using 2-diethylaminoethylamine in the same proportion, the *compound* formed colourless prisms from water, m. p. 154—156° (Found: C, 50·55; H, 7·65; N, 22·05.

$C_{13}H_{22}O_3N_6S$ requires C, 49·9; H, 7·4; N, 22·5%). The intermediate *acetamido*-derivative had m. p. 141—142° (Found: C, 50·7; H, 7·0; N, 19·95. $C_{15}H_{24}O_4N_6S$ requires C, 50·6; H, 7·0; N, 19·8%).

β-Sulphanilyl-α-acetylguanidine (II, R = H, R′ = Ac).—*p*-Nitrobenzenesulphonylguanidine (15 g., Roblin *et al.*, *loc. cit.*) and acetic anhydride (30 c.c.) were refluxed for ½ hour. The precipitate which formed after water had been added (40 c.c.) and the mixture allowed to stand was collected, warmed with ethanol, filtered off, and dried at 100°. The product (8·2 g.) without further purification was reduced in methanol (150 c.c.) with hydrogen at atmospheric pressure and temperature in the presence of Raney nickel (H_2 absorbed, 1970 c.c. Theory for $C_9H_{16}O_3N_6S$ at N.T.P., 2030 c.c.). Water (40 c.c.) was added to the methanol suspension which was then heated to the boil and filtered. On cooling, the *amine* crystallised out as colourless needles, m. p. 208—209° (Found: N, 21·4; S, 12·3. $C_9H_{12}O_3N_6S$ requires N, 21·9; S, 12·5%). It dissolved rapidly in cold dilute sodium hydroxide, but the solution on standing deposited colourless crystals of sulphanilylguanidine (no depression of m. p. when mixed with authentic specimen).

2-p-*Aminobenzenesulphonamidoiminazoline* (III, *n* = 2).—2-Methylthioiminazoline sulphate (4·1 g.) was added continuously during ½ hour to a mixture of N^1-acetylsulphanilamide (5·3 g.), sodium hydroxide (1 g.), and phenol (15 g.) stirred in an oil-bath maintained at 190—200°. The cooled melt was digested with excess of dilute sodium hydroxide solution, and the solid collected, washed thoroughly with water, and dried. Yield, 3·3 g.; m. p. 252—255°. Without further purification the solid was heated on the water-bath for 1½ hours in N-hydrochloric acid (16 c.c.). After being cooled, diluted with water, allowed to stand, and filtered from a little insoluble matter, the solution was made alkaline with ammonia. The precipitated *amine* gave colourless prisms from water (1·5 g.), m. p. 225·5—226·5° (Found: C, 45·45; H, 4·75; N, 23·2. $C_9H_{12}O_3N_4S$ requires C, 45·0; H, 5·0; N, 23·2%). The same compound was obtained in a similar manner starting directly from sulphanilamide, or from *p*-nitrobenzenesulphonamide followed by reduction of the nitro-group, but the yields were lower.

2-p-*Aminobenzenesulphonamidotetrahydropyrimidine* (III, *n* = 3).—Similarly prepared from N^1-acetylsulphanilamide (5·3 g.) and 2-methylthiotetrahydropyrimidine sulphate (5·4 g.) the *amine* formed colourless prisms (1·3 g.) from water, m. p. 239—240° (Found: C, 47·4; H, 5·35; N, 21·9. $C_{10}H_{14}O_3N_4S$ requires C, 47·3; H, 5·5; N, 22·1%).

2-p-*Aminobenzenesulphonamidothiazoline* (IV).—Similarly prepared from *N*′-acetylsulphanilamide (34·7 g.) and 2-methylthiothiazoline sulphate (29·5 g.), the *amine* formed colourless needles from aqueous ethanol (3·2 g.), m. p. 202—203·5° (Found: S, 25·1. Calc. for $C_9H_{11}O_3N_3S$: S, 24·9%). Sprague and Kissinger (*J. Amer. Chem. Soc.*, 1941, **63**, 578), who made the same compound by a route involving the use of a sulphonyl chloride, give m. p. 204—205°.

m-*Aminobenzenesulphonamidoguanidine* ("metanilylguanidine").—*m*-Nitrobenzenesulphonyl chloride (22·2 g.) in acetone (40 c.c.) was added during ½ hour to a solution of guanidine nitrate (12·2 g.) in 5N-sodium hydroxide (50 c.c.) stirred at 10—15°. After a further 1 hour the suspension was diluted with water (250 c.c.) and filtered, and the solid washed with ethanol and then recrystallised from water. The nitro-compound so obtained (11·2 g.) was stirred under reflux for 1 hour with a mixture of N-hydrochloric acid (110 c.c.) and iron filings (40 g.), and the suspension then made alkaline with sodium carbonate and filtered hot. On cooling, the *amine* crystallised in colourless needles. Further recrystallisation from water gave 1·8 g., m. p. 182—184° (Found: C, 39·25; H, 4·45; N, 25·65. $C_7H_{10}O_3N_4S$ requires C, 39·2; H, 4·7; N, 26·2%).

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[*Received, October 2nd*, 1946.]

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161. *A Relationship Between Viscosity, Density, and Vapour Pressure of Liquids.*

By LEO H. THOMAS.

An equation is proposed connecting the fluidity (ϕ) and the density (d) of a liquid with vapour pressure, and a comparison made of $\phi\sqrt{d}$ at corresponding pressures. The value of $\phi\sqrt{d}$ at the same reduced pressure is approximately a constant for all non-associated non-symmetrical substances. The significance of this constant is discussed.

IT was pointed out by Porter (*Phil. Mag.*, 1912, **23**, 458) that, for mercury and water, the logarithm of the viscosity (η) or fluidity is a linear function of the logarithm of the vapour pressure (p); *i.e.*, $\log_{10}\phi = b' + a'\log_{10}p$. Assuming the equation to hold up to the critical point, we may write

$$\log \phi/\phi_c = a'\log p/p_c \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ϕ_c and p_c are the critical fluidity and pressure respectively.

Graphically determined values of a' and b' are printed in Table I. It can be seen that for non-associated liquids, $a' \approx 0{\cdot}238$. Hence, in general, non-associated liquids in equilibrium with their vapours at the same reduced pressure have approximately the same reduced fluidity.

For highly symmetrical molecules, a' is found to be appreciably greater than 0·238, indicating that even at corresponding pressures, such substances are considerably more viscous than those possessing non-symmetrical molecules.

In a previous publication (*J.*, 1946, 573) the author discussed the relationship between viscosity and reduced temperature T_c and put forward the equation

$$\log\left[\frac{\eta\sqrt{v}}{\eta_c\sqrt{v_c}}\right] = k\left[\frac{T_c}{T} - 1\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where v is the specific volume at absolute temperature T, or,

$$\log_{10}\eta\sqrt{v} = \alpha + \beta/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It was also shown that $\eta_c\sqrt{v_c} \approx 1{\cdot}167$ (η in 10^3 poise); but log p is a linear function of $1/T$ (below) and therefore

$$\log_{10}\phi\sqrt{d} = b + a\log_{10}p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

or, introducing the critical pressure,

$$\log\phi\sqrt{d}/\phi_c\sqrt{d_c} = a\log p/p_c \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

which is a modification of (1).

Values of a, b, and log $\phi_c\sqrt{d_c}$ are also given in Table I. The introduction of $\sqrt{d}$ into the variable ϕ somewhat alters the slope so that $a \approx 0{\cdot}220$. The average deviation of a' from the mean 0·238 is 3·8% as compared with 4·2% deviation of a from the mean 0·220 for the same 46 liquids. However, unlike ϕ_c which is approximately constant only for one particular homologous series, $\phi_c\sqrt{d_c}$ is tolerably constant for all the non-associated liquids examined irrespective of type.

The fair constancy of a implies, of course, that at corresponding pressures, all the liquids—with the exception of those possessing highly symmetrical molecules—have approximately the same reduced value of $\phi\sqrt{d}$. Further, since $\log_{10}\phi_c\sqrt{d_c} \approx 2{\cdot}901$, the value of $\phi\sqrt{d}$ for a particular substance depends primarily on its " distance " from the critical state.

It should be pointed out that (5) leads to a value of 1·256 (η in 10 poise) for $\eta\sqrt{v}$ whereas (2) gives 1·167—a difference of 8%. Measurements in the region of the normal b. p. to the critical point, which at present are lacking, might therefore decide between (2) and (5) if indeed either equation represents the true viscosity behaviour in this region.

The nature of the experimental data is such as to necessitate calculation of a and b by the following methods:

(A) Actual vapour pressures at 10° intervals have been taken from the literature, and corresponding viscosities from Thorpe and Rodger (*Phil. Trans.*, 1894, **185**, 397; 1897, **189**, 71).

(B) When vapour pressures have been recorded only in the form of the equafion log $p = A - B/T$, a and b have been calculated from the values of α and β (Thomas, *loc. cit.*) and A and B. The percentage agreements between the calculated and the experimental values of $\eta\sqrt{v}$ are then necessarily the same as those involved in (3) which, with the corresponding temperature ranges, have previously been given (*ibid.*).

(C) For other liquids, vapour pressures have been recorded in the form of other p–T equations such as that of Dupré and Kirchoff, *viz.*: log $p = C - D/T - F\log T$. Vapour pressures corresponding to the experimental viscosities have then been calculated from these equations.

(D) In a few cases, vapour pressures have been mathematically interpolated from p–T tables for temperatures corresponding to the viscosity data.

The procedure adopted for a particular substance is indicated in the table by use of the above letters. Values of a and b recorded under (A), (C), and (D) have been evaluated by application of Campbell's " zero sum " method (*Phil. Mag.*, 1920, **39**, 177; 1924, **47**, 816). The measure of agreement between the experimental values of $\eta\sqrt{v}$ and those calculated from (4) is shown in col. 10. Corresponding deviations from (3) over the same temperature ranges are tabulated in the preceding column. Vapour pressure references are given as footnotes to the table; viscosity references have previously been given (*loc. cit.*).

Discussion of Results.—It is well known that often great discrepancies exist between vapour pressure measurements of different observers, especially the lower values, such differences arising partly from the use of insufficiently purified materials (Ramsay and Young, *J.*, 1885, 44). Large errors may also arise in the " static " method due to insufficient preliminary degassing of the material. Perhaps extreme cases are those of *o*- and *p*-xylenes. The values from 80° to 130° of Woringer (International Critical Tables) do not even approximately fall on the same p–T curve as that constructed from the data of Kassel (*loc. cit.*). Accordingly two values of a and b are recorded for *o*- and *p*-xylenes; they are seen to differ very widely indeed.

TABLE I.

	b'.	a'.	$\log_{10}\phi_c$.	b.	a.	Deviation, % in a.	a, calc., from b. p.	Deviation, % in a (from b. p.).	Mean % error, eqn. (4).	Mean % error, eqn. (3).	$\log_{10}\phi_c\sqrt{d_c}$.	Deviation, % in $\phi_c\sqrt{d_c}$.	Approx. temp. range.		Ref.
Propane	—	—	—	1·900	0·229	4·1	0·208	5·5	—	—	2·932	7·4	—	B	1
Butane	—	—	—	1·952	0·213	3·2	0·197	10·4	—	—	2·897	0·9	—	B	1
*iso*Butane	—	—	—	1·717	0·262	19·1	0·224	1·8	—	—	2·884	4·0	—	B	1
Pentane	2·002	0·241	3·062	1·953	0·221	0·4	0·210	4·5	—	—	2·925	5·7	—	B	1
*iso*Pentane	2·017	0·230	3·028	1·8994	0·2332	6·0	0·215	2·3	0·1	0·1	2·924	5·4	0—30°	A	1
Hexane	2·015	0·231	3·020	1·960	0·215	6·0	0·210	4·5	—	—	2·896	1·2	—	B	1
Heptane	2·031	0·230	3·022	1·9650	0·2169	1·4	0·215	2·3	0·4	0·4	2·900	0·2	0—90	A	1
Octane	2·027	0·230	3·010	1·9592	0·2183	0·8	0·221	0·4	0·7	0·3	2·891	2·3	20—120	A	1
Methyl formate	1·821	0·237	2·924	1·8687	0·2182	0·8	0·223	1·4	0·1	0·1	2·883	4·2	0—30	A	1
Methyl acetate	1·898	0·232	2·952	1·9235	0·2155	2·4	0·232	5·5	0·2	0·2	2·903	0·5	0—50	A	1
Ethyl acetate	1·906	0·236	2·958	1·9135	0·2213	0·6	2·238	8·2	0·3	0·1	2·899	0·5	0—70	A	1
Propyl formate	1·841	0·244	2·935	1·8520	0·2296	4·4	0·243	10·4	0·1	0·1	2·880	5·0	0—70	A	1
Methyl propionate	1·922	0·230	2·951	1·9345	0·2129	3·2	0·229	4·1	0·2	0·1	2·887	3·3	0—70	A	1
Ethyl propionate	1·940	0·232	2·961	1·9421	0·2136	2·9	0·235	6·8	0·3	0·1	2·882	4·5	0—80	A	1
Propyl acetate	1·887	0·247	2·973	1·8803	0·2328	5·8	0·245	11·3	0·8	0·1	2·904	0·7	20—100	A	1
Methyl butyrate	1·901	0·241	2·965	1·8887	0·2327	5·8	0·244	10·9	0·6	0·2	2·916	3·5	0—100	A	1
Methyl *iso*butyrate	1·893	0·244	2·969	1·8960	0·2268	3·1	0·236	7·3	0·6	0·1	2·896	1·2	0—90	A	1
Ethyl ether	2·000	0·237	3·046	1·9839	0·2169	1·4	0·208	5·5	0·3	0·1	2·899	0·5	0—30	A	1
Methyl propyl ether	1·996	0·235	—	2·010	0·215	2·3	0·213	3·2	—	—	—	—	—	B	1
Ethyl propyl ether	1·993	0·234	3·019	1·9558	0·2214	0·6	0·222	0·9	0·4	0·1	2·925	5·7	0—60	A	1
Propyl ether	1·955	0·246	—	1·919	0·231	5·0	0·229	4·1	—	—	—	—	—	B	1
Butyl ether	—	—	—	1·914	0·231	5·0	0·233	5·9	—	—	—	—	—	B	2
Methyl cyanide	—	—	—	1·9773	0·2100	4·5	0·207	5·9	0·1	0·2	2·934	7·9	16—77	C	3
Ethyl cyanide	—	—	—	1·9881	0·2071	5·9	0·206	6·4	0·0	0·1	2·920	4·5	20—93	C	3
Propyl cyanide	—	—	—	1·9053	0·2242	1·9	0·224	1·8	0·3	0·2	2·903	0·5	18—113	C	3
Butyl cyanide	—	—	—	1·9000	0·2225	1·1	0·225	2·3	0·2	0·2	—	—	19—134	C	3
Ethyl bromide	1·803	0·233	—	1·9167	0·2194	0·3	0·208	5·5	0·1	0·1	—	—	0—30	A	1
Propyl bromide	1·825	0·228	—	1·910	0·217	1·4	0·216	1·8	—	—	—	—	—	B	1
*iso*Propyl bromide	1·758	0·250	—	1·850	0·234	6·4	0·228	3·6	—	—	—	—	—	B	1
Nitromethane	1·820	0·243	—	1·894	0·217	1·4	0·224	1·8	—	—	—	—	—	B	1
Nitroethane	—	—	—	1·855	0·226	2·7	0·231	5·0	—	—	—	—	—	B	4
Nitropropane	—	—	—	1·8632	0·2249	2·2	0·236	7·3	0·5	0·2	—	—	15—122	C	5
Nitrobutane	—	—	—	1·9110	0·2134	3·0	0·233	5·9	0·8	0·4	—	—	15—143	C	5
Propyl chloride	1·844	0·249	—	1·875	0·227	3·2	0·218	0·9	—	—	2·905	0·9	—	B	1
*iso*Propyl chloride	1·771	0·273	—	1·799	0·251	14·1	0·237	7·2	—	—	—	—	—	B	1
Benzene*	1·616	0·301	2·988	1·6049	0·2925	—	0·291	—	0·3	0·4	2·937	8·9	0—80	A	6
Toluene	1·900	0·244	2·998	1·8928	0·2265	3·0	0·227	3·2	0·3	0·2	2·911	2·3	30—100	A	1
Ethylbenzene	1·858	0·264	—	1·8604	0·2436	10·7	0·214	2·7	0·3	0·2	—	—	0—130	A	1
o-Xylene	1·845	0·264	—	1·8931	0·2258	2·6	0·228	3·6	0·2	0·3	—	—	0—80	A	7
o-Xylene	—	—	—	1·8512	0·2419	—	—	—	0·1	0·1	—	—	90—140	A	1

p-Xylene	1·890	0·267		2·0061	0·1986	9·7	0·214	2·7	0·2	0·1	—	—	10—80	A	7
p-Xylene	,,	,,	—	1·8806	0·2479	—	,,	,,	0·1	0·1	—	—	90—130	A	1
m-Xylene	2·018	0·219	—	2·0213	0·1968	10·5	0·205	6·8	0·4	0·2	—	—	0—130	A	1
Methyl iodide	1·726	0·230	—	1·9373	0·2194	0·2	0·209	5·0	0·0	0·0	—	—	0—30	A	1
Ethyl iodide	1·775	0·225	—	0·9500	0·2099	4·6	0·205	6·8	0·2	0·2	—	—	0—60	A	1
Propyl iodide	1·789	0·225	—	1·926	0·215	2·3	0·212	3·6	—	—	—	—	—	B	1
*iso*Propyl iodide	1·739	0·241	—	1·873	0·232	5·5	0·222	0·9	—	—	—	—	—	B	1
Acetone	1·985	0·224	3·005	1·9763	0·2052	6·7	0·210	4·5	0·0	0·1	2·909	1·9	10—50	A	1
Methyl ethyl ketone	1·935	0·232	—	1·9241	0·2144	2·5	0·226	2·7	0·4	0·1	—	—	10—50	A	8
Methyl propyl ketone	—	—	—	1·931	0·218	0·9	0·218	0·9	—	—	—	—	—	B	8
Acetaldehyde	2·011	0·223	—	2·019	0·201	8·6	0·204	7·3	—	—	—	—	—	B	1
Butaldehyde	—	—	—	1·869	0·225	2·3	0·231	5·0	—	—	—	—	—	B	2
Methyl sulphide	1·957	0·220	2·973	1·9675	0·2024	8·0	0·200	9·1	0·2	0·1	2·903	0·5	0—30	A	1
Ethyl sulphide	1·906	0·246	2·906	1·8913	0·2354	7·0	0·211	4·1	0·2	0·1	2·944	10·4	10—80	A	1
Methylene chloride	1·754	0·239	2·857	1·8597	0·2224	1·1	0·216	1·8	0·1	0·1	2·884	4·0	0—30	A	1
Chloroform	1·734	0·234	2·815	1·8590	0·2162	1·7	0·216	1·8	0·3	0·1	2·858	10·4	0—60	A	1
Carbon tetrachloride *	1·383	0·318	2·825	1·5232	0·3018	—	0·293	—	0·1	0·3	2·890	2·6	20—70	A	1
Ethylene chloride *	1·581	0·279	2·866	1·677	0·258	—	0·270	—	—	—	2·864	8·9	—	B	1
Ethylene chloride	,,	,,	,,	1·625	0·278	—	,,	—	—	—	2·905	0·9	—	B	1
Ethylidene chloride	1·743	0·251	2·897	1·817	0·233	5·9	0·237	7·7	—	—	2·889	2·8	—	B	1
Ethylidene chloride	,,	,,	,,	1·803	0·241	9·5	,,	,,	—	—	2·911	2·3	—	B	1
s-Tetrachlorethane *	1·619	0·302	—	1·612	0·300	—	0·300	—	—	—	—	—	—	B	1
Styrene	—	—	—	1·9452	0·2258	2·6	0·223	1·4	1·0	1·7	—	—	0—140	C	9
*β-iso*Amylene	—	—	—	2·058	0·202	8·2	0·192	12·7	—	—	2·948	11·4	—	B	2
Isoprene	—	—	—	2·035	0·206	6·4	0·195	11·3	—	—	—	—	—	B	2
Fluorobenzene	1·782	0·258	2·951	1·8026	0·2475	12·5	0·246	11·8	0·5	0·6	2·925	5·7	0—81	D	6
Chlorobenzene	1·852	0·241	2·943	1·9142	0·2155	2·4	0·223	1·4	0·5	0·5	2·891	2·3	0—120	D	6
Bromobenzene	1·795	0·241	2·886	1·9250	0·2135	2·9	0·223	1·4	0·9	0·6	2·892	2·1	28—142	D	6
Iodobenzene	1·790	0·229	2·804	1·9351	0·2122	3·5	0·227	3·2	0·3	0·5	2·896	1·2	28—149	D	6
Nitrobenzene	—	—	—	1·894	0·209	5·0	0·216	1·8	—	—	—	—	—	B	1
Acetic anhydride	—	—	—	1·944	0·206	6·4	0·236	7·3	—	—	—	—	—	B	1
Propane-1-thiol	—	—	—	1·901	0·218	0·9	0·213	3·2	—	—	—	—	—	B	10
*cyclo*Hexene *	—	—	—	1·497	0·317	—	0·271	—	—	—	—	—	—	B	11
Ethylene bromide *	1·497	0·275	—	1·670	0·268	—	0·261	—	—	—	—	—	—	B	1
Dioxan *	—	—	—	1·4374	0·3126	—	0·324	—	0·3	0·5	—	—	0—80	A	12
Diphenyl	—	—	—	1·8567	0·2413	9·7	0·251	14·1	0·1	0·1	—	—	139—210	C	13
*cyclo*Hexane *	—	—	—	1·2495	0·3677	—	0·354	—	0·9	0·6	2·899	0·5	11—76	C	14
Ethylene oxide	1·891	0·227	—	1·9134	0·2082	5·4	0·211	4·1	0·4	0·5	—	—	−50—+9	D	1
Average values	—	0·238	—	—	0·220	4·2	—	5·2	0·33	0·25	2·901	3·5	—	—	—

* These symmetrical substances were excluded when calculating the mean values of a and a' and the deviations from them.

(1) *I.C.T.*
(2) Kuchinskaya, *Khim. Referat. Zhur.*, 1939, **2**, No. 4, 23.
(3) Heim, *Bull. Soc. chim. Belg.*, 1933, **42**, 467.
(4) Goodeve, *Trans. Faraday Soc.*, 1934, **30**, 501.
(5) Hodge, *Ind. Eng. Chem.*, 1940, **32**, 748.
(6) Young, *Sci. Proc. Roy. Dublin Soc.*, 1910, **12**, 374.
(7) Kassel, *J. Chem. Physics*, 1936, **4**, 276.
(8) Mayberry and Aston, *J. Amer. Chem. Soc.*, 1934, **56**, 2682.
(9) Patnode and Scheiber, *ibid.*, 1939, **61**, 3449.
(10) Taylor and Layng, *J. Chem. Physics*, 1933, **1**, 798.
(11) Harrison and Berg, *Ind. Eng. Chem.*, 1946, **38**, 117.
(12) Crenshaw, Cope, Finkelstein, and Rogan, *J. Amer. Chem. Soc.*, 1938, **60**, 2308.
(13) Chipman and Peltier, *Ind. Eng. Chem.*, 1929, **21**, 1106.
(14) Nagornov, *Chem. Zentr.*, 1927, ii, 2668.

Fairly large errors in a might also be expected to arise from the viscosity measurements. It is instructive to compare the data of Thorpe and Rodger (*locc. cit.*) for benzene with those of Bingham and Harrison (*Z. physikal. Chem.*, 1909, **66**, 1). Taking the same vapour pressure over the range 0—70°, the a value of the latter is 2% higher than that calculated from the viscosities of the former.

It seems probable then that errors in a of from 2 to 6% may reasonably be expected.

Of the 74 liquids examined, 66 show a mean error in a of 4·2%, of which 61 show errors of $< 7\%$. The remaining 8 liquids—unsubstituted ring compounds and certain of the polyhalides—are quite exceptional, this being due apparently to the fact that they all possess highly symmetrical molecules. The introduction of even one substituent group into the ring effectively destroys the symmetry and normal values of a are then exhibited.

Over a relatively small temperature range, it can hardly be expected that (4) would reproduce the experimental data as accurately as (3), for experimental errors in the determination of vapour pressure are superimposed on those incurred in the viscosity measurements. In fact, the average deviations are 0·33% and 0·25% respectively for the same 47 liquids.

Now

$$\frac{\mathrm{d}\log_e \phi\sqrt{d}}{\mathrm{d}\log_e p} = \frac{\mathrm{d}\log_e \phi\sqrt{d}}{\mathrm{d}(1/T)} \times \frac{\mathrm{d}(1/T)}{\mathrm{d}\log_e p} = a$$

and it has been shown (Thomas, *loc. cit.*) that $\mathrm{d}\log \phi\sqrt{d}/\mathrm{d}(1/T)$ (β) is sensibly constant only at temperatures near the b. p., but increases at lower temperatures. However, it is well known that $\mathrm{d}(1/T)/\mathrm{d}\log p$ *decreases* at lower temperatures (below). The effects are therefore compensatory; possibly, then, over more extended ranges, (4) may be more accurate than (3). Unfortunately, the necessarily low vapour pressures of those substances showing a noticeable increase in β at the lower temperatures, are not available. It is hoped to make this the subject of immediate experimental study.

From the Clapeyron equation we get

$$\mathrm{d}\log_e p/\mathrm{d}(1/T) = -LT/p(V_v - V_l)$$

where L is the g.-molar latent heat of vaporisation and V_v and V_l are the g.-molar volumes of vapour and liquid, respectively.

At temperatures up to the b. p., $V_v \gg V_l$. Assuming the perfect gas laws to hold for the saturated vapour, we may therefore write $\mathrm{d}\log_e p/\mathrm{d}(1/T) = -L/\boldsymbol{R}$.

The gas laws do not in fact apply to saturated vapours except at temperatures well below the b. p. as is shown by the observation of Young and Thomas (*J.*, 1893, **63**, 1191) that at a reduced pressure of 0·04423 the ratio of the actual vapour densities to the theoretical values for ten lower esters is $\sim 1{\cdot}06$. It is suggested that the equation

$$\mathrm{d}\log_e p/\mathrm{d}(1/T) = -E/\boldsymbol{R} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

or

$$\log_e p = A - E/\boldsymbol{R}T$$

represents liquid–vapour equilibrium, where E is a quantity greater than L at the b. p. or somewhat below the b. p. and becoming equal to L only at still lower temperatures.

Between the b. p. and the critical point, (6) is found to hold with fair accuracy even though L rapidly decreases with rising temperature to zero *at* the critical point. The table below, compiled from the data in the I.C.T., shows the average percentage deviations between observed pressures and those calculated from (6) for twelve substances at 10° intervals between their b. p.s and critical points.

Carbon tetrachloride	0·7	Octane	0·5	Hexane	0·5
Pentane	0·2	Xenon	0·4	Ethyl propionate	0·8
Methyl butyrate	0·8	Benzene	0·7	*cyclo*Hexane	0·5
Chlorobenzene	0·3	Ethyl acetate	0·8	Heptane	0·6

(Mean deviation = 0·6%.)

A recent publication by Gouq-jen Su (*Ind. Eng. Chem.*, 1946, **38**, 923) shows a graph of $\log p/p_c$ against T_c/T for a number of substances for P/p_c values of 0·001 to unity. The plots show no noticeable curvature.

From the above relationships, $E = \boldsymbol{L}RT/p(V_v - V_l)$. Values of this function are printed

below. Vapour pressures and molar volumes were taken from I.C.T. The latent heats used are those based on direct calorimetric data.

t.	$E/10$, cals. per mole.	Devn., %, from mean.	t.	$E/10$, cals. per mole.	Devn., %, from mean.	t.	$E/10$, cals. per mole.	Devn., %, from mean.	t.	$E/10$, cals. per ole.	Devn., %, from mean.
Benzene (t_c = 288°).			*Benzene* (t_c = 288°).			*Carbon dioxide* (t_c = 31°).			*Carbon dioxide* (t_c = 31°).		
100°	727	+1·2	200°	707	−1·5	−30°	384	−0·8	0°	390	+0·8
120	728	+1·2	220	715	−0·4	−25	386	−0·3	5	385	−0·5
140	722	+0·6	240	727	+1·2	−20	391	+1·0	10	380	−1·8
160	711	−1·0	260	742	+3·3	−15	395	+2·0	15	383	−1·0
180	711	−1·0	280	757	+5·5	−10	395	+2·0	20	377	−3·0
						− 5	393	+1·5	25	350(?)	

The average deviations from the mean values are 1·3% for benzene (100—260°) and 1·3% for carbon dioxide (− 30° to + 20°). The large *positive* deviation for benzene and the large *negative* deviation for carbon dioxide at the two top temperatures might well be due to experimental errors in the difficult determinations of latent heats, vapour pressures, and specific volumes. For temperatures between the b. p. and the critical point the error involved in (6) does not then *demonstrably* exceed the probable experimental error.

At temperatures somewhat below the b. p., $-\mathrm{d}\log_e p/\mathrm{d}(1/T)$ becomes $\approx L/R$, and therefore E slowly increases with fall in temperature.

The fair constancy of E would seem to imply that it represents some fundamental characteristic of liquid–vapour equilibria. In general, it cannot be equated to L except presumably at temperatures sufficiently below the b. p.

Since the constants in Table I were evaluated by means of logarithms to the base 10, (6) becomes :

$$\log_{10} p = A/2{\cdot}303 - E/2{\cdot}303\,RT$$

but

$$\log_{10} \eta\sqrt{v} = -b - a\log_{10} p$$

therefore

$$\log_{10} \eta\sqrt{v} = -b - aA/2{\cdot}303 + aE/2{\cdot}303\,RT = \alpha + \beta/T$$

therefore $a = 2{\cdot}303\,R\beta/E = 4{\cdot}571\,\beta/E$. But $\beta = E_{\text{visc.}}/2{\cdot}303R$, where $E_{\text{visc.}}$ is the activation energy of viscous flow defined by the equation

$$\eta\sqrt{v} = \text{constant} \times e^{E_{\text{visc.}}/RT}$$

Therefore $a = E_{\text{visc.}}/E$, or, at temperatures somewhat lower than the b. p., $a = E_{\text{visc.}}/L$.

It has been shown by Kistiakowsky (*Z. physikal. Chem.*, 1923, **107**, 65) that the value of L in calories at the b. p., T_B, is given by

$$L = 2303\,RT_B \log_{10} 82{\cdot}07\,T_B$$

The relationship holds with a satisfactory degree of accuracy (the average percentage error between $L_{\text{calc.}}$ and $L_{\text{obs.}}$ is 3%) over a b. p. range of − 196° for nitrogen to 1554° for silver chloride which includes fused metals and salts. It is not obeyed for associated liquids such as alcohols. Therefore $a \approx \beta/T_B \log_{10} 82{\cdot}07\,T_B$.

The mean value of a so determined is 0·245, being higher than the previous value 0·220 owing to the fact that $L < E$. For purposes of comparison the values of a in col. 8 have been obtained by multiplying the values calculated as above by the factor 0·220/0·245 = 0·8975, so that

$$a \approx 0{\cdot}8975\,\beta/T_B \log_{10} 82{\cdot}07\,T_B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

or

$$E = 5{\cdot}093\,T_B \log_{10} 82{\cdot}07\,T_B$$

In addition to the above tabulated values, Table II has been compiled from (7) for a number of substances whose vapour pressures have not been determined.

As mentioned above, (3) is accurate only at temperatures approaching the b. p., and at lower temperatures the plots of $\log \eta\sqrt{v}$–$1/T$ are decidedly convex to the $1/T$ axis (see graph, Thomas, *loc. cit.*). Within the approximate temperature range 0—100° therefore the β values of

TABLE II.

Substance.	*a*.	Substance.	*a*.
*iso*Pentane	0·215	Amyl cyanide	0·225
*iso*Hexane	0·214	Phenyl cyanide	0·213
*iso*Heptane	0·214	Benzyl cyanide	0·220
Nonane	0·230	Ethyl ketone	0·213
Ethyl valerate	0·238	Propionic anhydride	0·239
Butyl propionate	0·239	Allyl chloride	0·218
Butyl bromide	0·212	Allyl bromide	0·214
*iso*Butyl bromide	0·233	Allyl iodide	0·212
Amyl bromide	0·215	Diallyl	0·213
Hexyl bromide	0·223	Nitropentane	0·236
Heptyl bromide	0·231	Nitro*iso*pentane	0·256
Butane-1-thiol	0·216	Propyl nitrite	0·216
Pentane-1-thiol	0·217	Butyl nitrite	0·222
Pentane-2-thiol	0·223	Amyl nitrite	0·220
Hexane-2-thiol	0·220	*iso*Amyl nitrite	0·210
Hexane-1-thiol	0·223	Anisole	0·257
Heptane-1-thiol	0·231	Phenetole	0·246
Heptane-2-thiol	0·231	*o*-Chlorotoluene	0·223
*iso*Butyl iodide	0·224	*m*-Chlorotoluene	0·211
*iso*Butyl chloride	0·241	*m*-Bromotoluene	0·215
Propaldehyde	0·249	*p*-Bromotoluene	0·209
*iso*Valeraldehyde	0·247	Acetophenone	0·223
Methylene bromide	0·207	Methyl*cyclo*hexane	0·251

(Mean % deviation from $a = 0{\cdot}220$ is 4·9.)

liquids of sufficiently high b. p. will be too great to correspond with the values of E calculated from (7). High values of a are then to be expected :

Decane	0·239	Octyl bromide	0·241
Undecane	0·244	Octane-1-thiol	0·240
Dodecane	0·254	Propylene bromide	0·253
Butyl valerate	0·247	*iso*Butylene bromide	0·286
Ethyl heptoate	0·249	*p*-Methyl*cyclo*hexanone	0·263
Heptyl acetate	0·264		

These are precisely those higher-boiling liquids which show large (1—2%) errors in equation (3).

The data for symmetrical substances in Table I are scanty. They may be supplemented to a certain extent by the following values calculated from (7) :

Thiophen	0·253	*cyclo*Hexanone	0·311
*cyclo*Hexene	0·271	*cyclo*Hexyl chloride	0·281
Chloral	0·283	*cyclo*Hexyl bromide	0·269

The high values exhibited by *cyclo*hexanone and by the *cyclo*hexyl halides are surprising in view of the fact that the benzenoid analogues of the latter are normal. The case of chloral seems anomalous. Clearly, further experimental study is necessary before the effect of molecular symmetry can be confidently assessed.

Assuming $a = 0{\cdot}220$, (7) enables one to calculate β for a given compound from its b. p. at atmospheric pressure with an average error of $\sim 5\%$. By using this value ($\beta_{calc.}$), $\eta\sqrt{v}$ at any temperature T_2 may be calculated from one measured value at another temperature T_1 by the use of (3).

It may easily be shown that the error in $\log(\eta\sqrt{v})_{T_2}$ is given by

$$\Delta \log \eta\sqrt{v} = \Delta\beta\,[1/T_2 - 1/T_1]$$

where $\Delta\beta$ is the difference between $\beta_{calc.}$ and the actual value.

Between 0° and 100° the above becomes $\Delta \log \eta\sqrt{v} = 0{\cdot}000982\,\Delta\beta$. Putting $\beta = 400$ (*e.g.*, from butane to nonane, β increases from 261 to 492), we have

$$\Delta \log \eta\sqrt{v} = 20 \times 0{\cdot}000982 = 0{\cdot}01964 \text{ or } \Delta\,\eta\sqrt{v} = 4{\cdot}6\%$$

The error involved in this procedure will naturally be $>$ or $<$ 4·6% according as $\beta >$ or < 400.

A treatment similar to that above, but involving the internal latent heat L_i, has been given by Eyring *et al.* (an excellent review of which is given by Kincaid, Eyring, and Stearn, *Chem. Rev.*, 1941, **28**, 301), who have developed a general theory of the liquid state.

The activation energy of viscous flow $E_{visc.}$ [which equals $\boldsymbol{R}$ d $\log_e\eta/\mathrm{d}(1/T)$] is regarded as that required for the formation of a " hole " into which the unit of flow can be transferred by rotation. The theorem is derived that " the energy necessary to make a hole in the liquid the size of a molecule equals the energy of vaporisation (the internal latent heat of vaporisation) ". The hole necessary for viscous flow will in general be a fraction of the full size of the molecule, the fraction depending on the shape of the flowing unit; $E_{visc.}$ will then be some fraction of L_i such that $L_i/E'_{visc.} = n$. For normal molecules, $n \approx 4$, but for symmetrical molecules, $n \approx 3$.

The values of L_i used were those at the b. p. Now, L_i increases quite rapidly as the temperature drops from the b. p.; for instance, for benzene, from 80° to 0° there is an increase in L_i of 17%. Presumably, if viscosity measurements were conducted over a given temperature range, then the mean value of L_i over that range should have been used.

Between the b. p. and the critical point, L_i of course decreases to zero at the latter temperature. If n is taken to be constant, then $E_{visc.}$, and hence the slope of the log η–$1/T$ curve, should likewise decrease to zero. The only substance on which viscosity measurements have been carried out in this range is carbon dioxide. Solution of (3) gives $\alpha = -0{\cdot}8519$ and $\beta = 513{\cdot}7$, between 5° and 29°. The average agreement between viscosity calculated from these constants and the experimental values is 1·0%, showing that a sensibly linear relationship holds.

The treatment given in this paper is free from such objections since $\boldsymbol{R}\mathrm{d}\log_e p/\mathrm{d}(1/T) = E$ is constant, at least above the b. p. The physical significance to be attributed to E, beyond the fact that it can be equated to L at temperatures well below the b. p., is, however, not clear.

SCHOOL OF MINES AND TECHNOLOGY, TREFOREST. [*Received, July 9th*, 1946.]

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162. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXI. Derivatives of 2′ : 4′-Dinitrobenzene-2-naphthol-1-diazosulphonate.*

By (the late) F. M. ROWE and W. OSBORN.

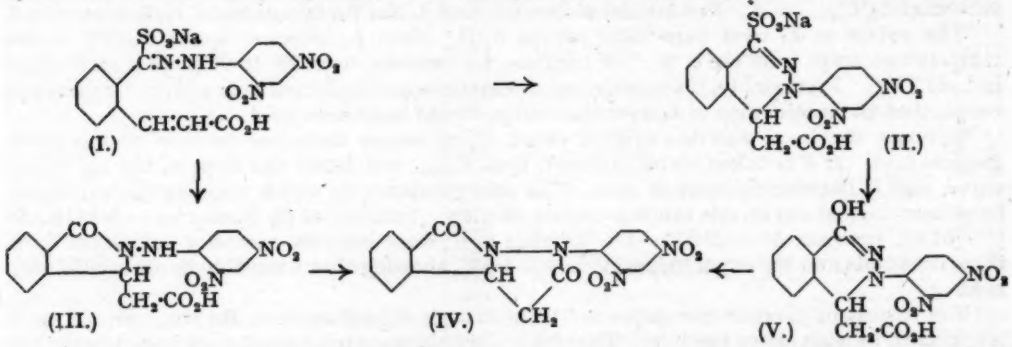
As a result of the presence of the two nitro-groups, sodium 1-(2′ : 4′-dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate is readily converted into *sodium benzaldehyde 2′ : 4′-dinitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid* (I), which is the most stable compound of this type yet examined (cf. Rowe, McFadyen, and Peters, this vol., p. 468). With aqueous sulphuric acid (b. p. 140°), *1-hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid* (V) behaves abnormally, giving *2-(2′ : 4′-dinitrophenylamino)isoindolinone-3-acetic acid* (III) and *1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine* (VIII); the latter is convertible by sulphuric acid at 180° into *2′ : 4′-dinitro-3-phenylphthalaz-4-one*. Other anomalies of this series of compounds are described and, where possible, derivatives of the 2′ : 4′-dinitro-series are correlated with analogues of the 2′- and 4′-nitro-series.

THE naphthalene ring in certain sodium 1-arylazo-β-naphthaquinone-1-sulphonates undergoes fission on addition of sodium hydroxide, with formation of sodium benzaldehyde arylhydrazone-ω-sulphonate-2-β-acrylic acids (Rowe *et al.*, *J.*, 1935, 1796; 1936, 1098). Under suitable conditions ring closure of these open-chain compounds can then be effected to yield either a 2-(nitroarylamino)*iso*indolinone-3-acetic acid, *via* a benzo-nitroarylhydrazide-2-β-acrylic acid, or a sodium hydrogen 3-(nitroaryl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate. This possibility of ring closure in one of two directions according to the conditions was originally thought to be limited to compounds containing a nitro-group in the 2′-position, but it has recently been shown that it can also be effected with compounds containing a nitro-group in the 4′-position (Rowe and Cross, *J.*, this vol., p. 461; Rowe, McFadyen, and Peters, *loc. cit.*). It appeared desirable therefore to examine the series of compounds derived from a sodium 1-arylazo-β-naphthaquinone-1-sulphonate containing nitro-groups in both the 2′- and the 4′-position to obtain further evidence with regard to the constitutions of the compounds and their inter-relationships.

Conversion of 2′ : 4′-dinitrobenzene-2-naphthol-1-diazosulphonate through sodium 1-(2′ : 4′-dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate into *sodium benzaldehyde 2′ : 4′-dinitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid* (I) proceeds readily, but much more 2′ : 4′-dinitrobenzeneazo-β-naphthol is formed than in analogous cases even at 0°, whilst above 10° complete conversion into 2′ : 4′-dinitrobenzeneazo-β-naphthol occurs.

A notable effect of the additional nitro-group is the remarkable stability of compound (I).

Whereas analogous sodium benzaldehyde nitroarylhydrazone-ω-sulphonate-2-β-acrylic acids are very rapidly converted by aqueous sodium hydroxide into the corresponding sodium hydrogen 3-(nitroaryl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetates, the most stable yet examined, *viz.*, the compound derived from 2 : 6-dichloro-4-nitroaniline (Rowe, McFadyen, and Peters, *loc. cit.*), being entirely converted within 3 hours from the addition to the sodium hydroxide, no *sodium hydrogen* 3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-

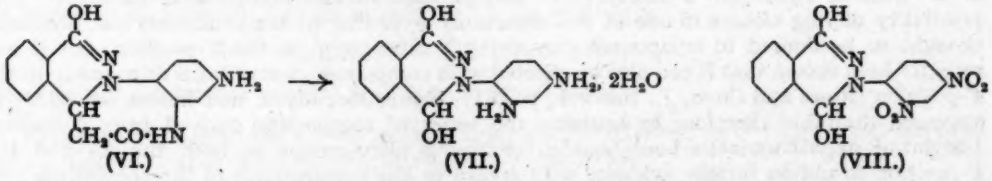


acetate (II) can be detected under 45 minutes from the addition of the sodium hydroxide, and traces of (I) are still present even after reaction with sodium hydroxide for 2 days. Moreover, boiling (I) with dilute hydrochloric acid for at least 12 hours is necessary for complete conversion into 2-(2′ : 4′-*dinitrophenylamino*)iso*indolinone*-3-*acetic acid* (III), and none of the intermediate benzo-2′ : 4′-dinitrophenylhydrazide-2-β-acrylic acid can be detected. Compound (III) could neither be nitrosated nor methylated, but the methylated compound, *methyl* 2-(2′ : 4′-*dinitrophenylmethylamino*)iso*indolinone*-3-*acetate*, was synthesised by condensing *o*-carboxycinnamonitrile *via* the acid chloride (*J.*, 1936, 1101) with 1-(2′ : 4′-dinitrophenyl)-1-methylhydrazine to form *benzo*-1′-(2″ : 4″-*dinitrophenyl*)-1′-*methylhydrazide*-2-β-*acrylonitrile*, followed by ring-closure and hydrolysis with methyl-alcoholic hydrogen chloride.

Water is eliminated from (III) with formation of 2 : 5-*diketo*-3-(2′ : 4′-*dinitrophenyl*)iso*indolinopyrazolidocoline* (IV) which is readily reconverted into (III) by diluting a solution in sulphuric acid. Concentrated or aqueous mineral acids have no action on (III) or (IV) except to open the pyrazole ring of the latter. Compound (IV) can also be obtained by nitrating the corresponding 2′- or 4′-nitrophenyl compounds, but (III) cannot be obtained by nitrating 2-(2′- or 4′-nitrophenylamino)*iso*indolinone-3-acetic acid.

Compound (IV) is reduced by iron and acetic acid to 2 : 5-*diketo*-3-(2′-*nitro*-4′-*aminophenyl*)-iso*indolinopyrazolidocoline* which could not be reduced further, nor could the pyrazole ring be opened by hydrolysis.

Compound (I) is completely converted into (II) by the action of aqueous sodium hydroxide at 0° for 6 days. Compound (II) is also more resistant to hydrolysis than are analogous compounds, and prolonged boiling with dilute hydrochloric acid is necessary for complete conversion into 1-*hydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (V). When (V) is refluxed with acetic anhydride and pyridine, (IV) is obtained eventually, although in not quite as good a yield as when (III) is similarly treated.



Compound (V) is reduced by stannous chloride and hydrochloric acid to 1-*hydroxy*-3-(2′ : 4′-*diaminophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid lactam* (VI), but the corresponding acid could not be obtained. When (VI) was refluxed with sulphuric acid (b. p. 140°), 1 : 4-*dihydroxy*-3-(2′ : 4′-*diaminophenyl*)-3 : 4-*dihydrophthalazine dihydrate* (VII) was formed. Attempts to remove the elements of water from the latter caused degradation of the compound, which could not be obtained by reduction of the corresponding dinitro-derivative (VIII).

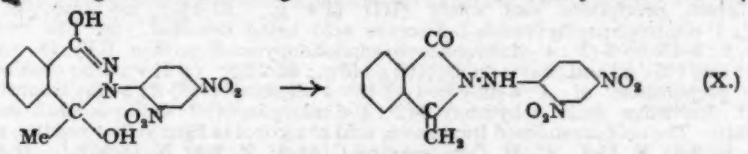
The action of mineral acids under various conditions on (V) was of considerable interest.

Refluxing (V) with sulphuric acid (b. p. 140°) gave a mixture of 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid (III) and 1 : 4-*dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* (VIII), this unusual result being clearly due to the presence of the two nitro-groups. 2-(2′ : 4′-Dinitrophenylamino)*iso*indolinone-3-acetic acid (III) was obtained whenever 1-hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (V) was treated with reagents which tend to attack the 3-nitrogen atom, *i.e.*, in all acid reactions or oxidations, and its formation involves an intermediate open-chain derivative, which is unstable and convertible into (III) under the conditions used.

The reason for the structure of (VIII) is clear when its reactions are considered. It will not form salts with mineral acids, or a picrate or perchlorate, and it cannot be dehydrated with the usual reagents, whilst concentrated sulphuric acid at 180° causes not only dehydration, but also simultaneous isomerisation to 2′ : 4′-*dinitro*-3-*phenylphthalaz*-4-*one*. Thus, the two nitro-groups in the nitrophenyl nucleus completely inhibit any salt formation on the 3-nitrogen atom. Consequently, dehydration with formation of the 3-arylphthalaz-1-one is impossible with a derivative of 2 : 4-dinitroaniline. A more convenient method of obtaining (III) and (VIII) was to add concentrated sulphuric acid to a boiling acetic acid solution of (V) and pour the solution into water. This method was examined with a number of 1-hydroxy-3-(nitroaryl)-3 : 4-dihydrophthalazine-4-acetic acids; all gave the nitro-3-phenylphthalaz-1-one satisfactorily, whilst 1-hydroxy-3-(4′-chloro-2′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid gave 2-(4′-chloro-2′-nitrophenylamino)*iso*indolinone-3-acetic acid in addition.

With concentrated sulphuric acid at 180° for 2—3 minutes, (V) gave the same compounds in diminished yield, whilst after 20 minutes the products were 2′ : 4′-dinitro-3-phenylphthalaz-4-one with some (III). Heating (V) with fuming hydrochloric acid at 180° gave 2′ : 4′-*dinitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* and a little (III), whilst fuming nitric acid or acid dichromate gave a mixture of 1 : 4-*dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine* (IX) and (III). On the other hand, fuming nitric acid converted 1-hydroxy-3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid into 4′-nitro-3-phenyl-4-methylphthalaz-1-one.

When 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (VIII) was treated with chromium trioxide in acetic acid solution at 40°, immediate oxidation to *phthalyl*-2′ : 4′-*dinitrophenylhydrazide* occurred, none of the intermediate 1 : 4-*diketo*-3-(2′ : 4′-*dinitrophenyl*) *tetrahydrophthalazine* being detected, although the latter was obtained by oxidation of (V) with

(IX.)  (X.)

potassium permanganate at 80°, whilst treatment of (V) with potassium permanganate at 60° gave 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid (III). Nitro-3-arylphthalaz-1-ones, however, were unaffected by chromium trioxide under similar conditions.

Heating (VIII) with dilute hydrochloric acid at 190° (*J.*, 1937, 90) gave 2′ : 4′-dinitro-3-phenylphthalaz-4-one together with an intermediate open-chain compound.

2′ : 4′-Dinitro-3-phenylphthalaz-4-one was synthesised from *o*-phthalaldehydic acid and 2 : 4-dinitrophenylhydrazine *via* o-*carboxybenzaldehyde* 2′ : 4′-*dinitrophenylhydrazone* (cf. *J.*, 1936, 312), but attempts to prepare it by nitrating 4′- or 2′-nitro-3-phenylphthalaz-4-one were unsuccessful.

1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine (IX) could not be methylated with methyl sulphate, but, when it was crystallised from methyl alcohol containing a trace of mineral acid, 1-*hydroxy*-4-*methoxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine* was formed, which was reconverted into (IX) by boiling ammonia. 1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (VIII), however, was readily methylated with methyl sulphate, and the primary product combines with alcohols to form ethers typical of the nitro-3-arylphthalaz-1-ones.

1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine (IX) was readily oxidised with chromium trioxide to phthalyl-2′ : 4′-dinitrophenylhydrazide, whereas 2′-, 3′-, or 4′-nitro-3-aryl-4-methylphthalaz-1-ones were unaltered. Treatment of (IX) with concentrated sulphuric acid at 180° caused dehydration and isomerisation to 2′ : 4′-dinitro-3-phenyl-1-methylphthalaz-4-one, whilst the action of dilute hydrochloric acid at 190° gave 2-(2′ : 4′-*dinitrophenylamino*)-3-*methylene*isoindolinone (X), which was readily converted into 2′ : 4′-dinitro-3-phenyl-1-methylphthalaz-1-one by heating with concentrated sulphuric acid at 180°.

Oxidation of (X) with chromium trioxide gave phthalyl-2′ : 4′-dinitrophenylhydrazide, whilst boiling alcoholic sodium ethoxide opened the ring with formation of *o-carboxyacetophenone-2′ : 4′-dinitrophenylhydrazide*, the latter being most readily prepared, however, by condensing acetophenone-*o*-carboxylic acid with 2 : 4-dinitrophenylhydrazine. The only method by which this hydrazide could be converted into 2′ : 4′-dinitro-3-phenyl-1-methylphthalaz-4-one was by heating with concentrated sulphuric acid at 180°.

In an attempt to synthesise 1 : 4-diketo-3-(2′ : 4′-dinitrophenyl)tetrahydrophthalazine (cf. Rowe, Gillan, and Peters, *J.*, 1935, 1811), phthalic anhydride was condensed with 2 : 4-dinitrophenylhydrazine in cold chloroform to form *o-carboxybenzo-2′ : 4′-dinitrophenylhydrazide*, which was converted by boiling with acetic acid into phthalyl-2′ : 4′-dinitrophenylhydrazide, but refluxing the latter with alcoholic sodium hydroxide merely gave *o*-carboxybenzo-2′ : 4′-dinitrophenylhydrazide.

Experimental.

Fuller details of preparation are given for the corresponding analogues (*J.*, 1926, 699; 1935, 1800; 1936, 1102).

Sodium Benzaldehyde 2′ : 4′-Dinitrophenylhydrazone-ω-sulphonate-2-β-acrylic Acid (I).—A filtered solution of commercial 50% sodium-β-naphthol-1-sulphonate (48 g.) in water (150 c.c.) was stirred rapidly at 0° into a solution of diazotised 2 : 4-dinitroaniline, prepared by stirring the base (18·3 g.) with a mixture of sodium nitrite (10 g.) and concentrated sulphuric acid (60 c.c.), leaving the resultant paste for 2 hours to form a clear brown solution, and then pouring it on ice (200 g.). 2′ : 4′-Dinitrobenzene-2-naphthol-1-diazosulphonate separated as a purplish-brown paste, which was filtered off, washed free from acid with ice-cold water, pasted with ice-cold water (120 c.c.), and treated with an ice-cold solution of sodium carbonate (30 g.) in water (100 c.c.). Almost colourless plates of sodium 1-(2′ : 4′-dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate began to separate from the pinkish-orange solution after 10 minutes, and the ice-cold suspension was then added to an ice-cold solution of sodium hydroxide (25 g.) in water (100 c.c.). In order to obtain the maximum yield, the thick bordeaux-red paste was acidified after 25 minutes with concentrated hydrochloric acid; it was then made alkaline and filtered from 2′ : 4′-dinitrobenzeneazo-β-naphthol (9 g.; 27·9%). The cold filtrate was faintly acidified with hydrochloric acid; on standing, the sodium hydrogen salt separated as a light sand-coloured precipitate, which crystallised from hot water in small orange-red prisms containing 1 mol. of H_2O (34 g.; 71·5% calc. on the 2 : 4-dinitroaniline) (Found: S, 6·6; H_2O, 3·7. $C_{16}H_{11}O_9N_4SNa,H_2O$ requires S, 6·7; H_2O, 3·8%). It is an orange acid dye, fugitive to light.

2-(2′ : 4′-*Dinitrophenylamino*)*iso*indolinone-3-*acetic Acid* (III).—(*a*) The preceding sodium salt (I) (5 g.) was dissolved in boiling water (200 c.c.), concentrated hydrochloric acid (20 c.c.) added dropwise during 2 hours, and boiling continued until evolution of sulphur dioxide had ceased (12 hours). The reddish-brown precipitate was solely (III) (2·4 g.; 61·4%), no trace of the intermediate benzo-2′ : 4′-dinitrophenylhydrazide-2-β-acrylic acid being detected. (*b*) The best method was to dissolve 2 : 5-diketo-3-(2′ : 4′-dinitrophenyl)*iso*indolinopyrazolidocoline (IV) (5 g.) in concentrated sulphuric acid (25 c.c.) and pour it on ice (100 g.) (5 g.; 95·2%). (*c*) It was also obtained as a by-product in the preparation of 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine and its 4-methyl derivative from 1-hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (see p. 834). The *acid* crystallised from acetic acid or alcohol in light yellow needles, m. p. 270° (Found: C, 51·7; H, 3·6; N, 15·1. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·3; N, 15·05%). It dissolves in sodium carbonate and sodium hydroxide solutions with yellowish-brown and deep crimson colours, respectively. It is unaltered by refluxing with aqueous sulphuric acid (b. p. 140°), but refluxing with alcoholic sulphuric or hydrochloric acid gives the ester. The *methyl* ester crystallised from methyl alcohol in light yellow plates, m. p. 183° (Found: C, 52·5; H, 4·0; N, 14·55. $C_{17}H_{14}O_7N_4$ requires C, 52·8; H, 3·65; N, 14·5%). The *ethyl* ester crystallised from ethyl alcohol in light yellow plates, m. p. 153° (Found: C, 53·9; H, 4·3; N, 14·3. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%). The *anilide* crystallised from acetic acid in yellow needles, m. p. 274° (Found: N, 15·8. $C_{22}H_{17}O_6N_5$ requires N, 15·65%).

2 : 5-*Diketo*-3-(2′ : 4′-*dinitrophenyl*)*iso*indolinopyrazolidocoline (IV).—(*a*) Compound (III) (30 g.) was refluxed with acetic anhydride (75 c.c.) and pyridine (3 c.c.) for 1 hour; the product crystallised on cooling (21 g.; 73·6%). (*b*) 2 : 5-Diketo-3-(2′-nitrophenyl)*iso*indolinopyrazolidocoline (1 g.) was treated with fuming nitric acid (*d* 1·5; 3 c.c.) at room temperature for 10 minutes, then poured on ice (10 g.) and the precipitate collected (1 g.; 87·6%). (*c*) 2 : 5-Diketo-3-(4′-nitrophenyl)*iso*indolinopyrazolidocoline (1 g.) was nitrated as described under (*b*) above (1·1 g.; 96·4%). (*d*) Compound (V) (10 g.) was refluxed with acetic anhydride (25 c.c.) and pyridine (1 c.c.) for 20 hours; the product crystallised on cooling (5·6 g.; 58·8%). The presence of pyridine was essential for this conversion, compound (V) being recovered unaltered in its absence. 2 : 5-*Diketo*-3-(2′ : 4′-*dinitrophenyl*)*iso*indolinopyrazolidocoline crystallised from acetic acid in light yellow, prismatic needles, m. p. 239° (Found: C, 54·2; H, 2·9; N, 15·6. $C_{16}H_{10}O_6N_4$ requires C, 54·25; H, 2·8; N, 15·8%), insoluble in cold dilute mineral acids or alkalis, but soluble in concentrated sulphuric acid, 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid being precipitated on diluting the solution.

2:5-*Diketo*-3-(2′-*nitro*-4′-*aminophenyl*)*iso*indolinopyrazolidocoline.—Compound (IV) (10 g.) was dissolved in acetic acid (300 c.c.), the solution diluted with water (60 c.c.), and then iron powder (6 g.) added to the boiling solution during 7 minutes. Boiling was continued for a further 3 minutes (charcoal), and the solution filtered hot; crystals separated on cooling. 2 : 5-*Diketo*-3-(2′-*nitro*-4′-*aminophenyl*)*iso*indolinopyrazolidocoline crystallised from aqueous acetic acid in orange, flat prisms, m. p. 276° (Found: C, 59·3; H, 3·85; N, 17·6. $C_{16}H_{12}O_4N_4$ requires C, 59·25; H, 3·7; N, 17·3%). It forms with concentrated mineral acids colourless, water-soluble salts, and the solutions readily diazotise and couple with β-naphthol to form a red dye. It neither forms a triazole derivative nor an anhydro-derivative by the

action of acids or phosphorus pentachloride. The *monoacetyl* compound crystallised from acetic anhydride in almost colourless prisms, m. p. 255° (Found: C, 58·9; H, 4·0; N, 15·0. $C_{18}H_{14}O_5N_4$ requires C, 59·0; H, 3·8; N, 15·3%). The nitro-group in 2 : 5-diketo-3-(2′-nitro-4′-aminophenyl)*iso*indolinopyrazolidocoline or its acetyl derivative could not be reduced satisfactorily, and the former could not be converted into 2-(2′-nitro-4′-aminophenylamino)*iso*indolinone-3-acetic acid by analogous means to those used with (IV).

Benzo-1′-(2″ : 4″-dinitrophenyl)-1′-methylhydrazide-2-β-acrylonitrile.—*o*-Carboxycinnamonitrile (0·5 g.) and phosphorus pentachloride (0·5 g.) were heated to 110° for 30 minutes; the phosphorus oxychloride was then distilled off under reduced pressure at 100°, and the solid residue of acid chloride dissolved in cold chloroform (10 c.c.) and filtered into a solution of 1-(2′ : 4′-dinitrophenyl)-1-methylhydrazine (0·7 g.) in chloroform (50 c.c.). The resultant orange suspension was boiled for 10 minutes, water (50 c.c.) and hydrochloric acid (1·5 c.c.) were added, and chloroform was distilled off and the precipitate collected. The *nitrile* crystallised from methyl alcohol in long, colourless, flat prisms, m. p. 189° (1 g.; 94·3%) (Found: C, 55·8; H, 3·65; N, 19·1. $C_{17}H_{13}O_5N_5$ requires C, 55·6; H, 3·6; N, 19·1%).

Methyl 2-(2′ : 4′-Dinitrophenylmethylamino)isoindolinone-3-acetate.—The above nitrile (0·5 g.) was suspended in dry methyl alcohol (20 c.c.) and saturated with dry hydrogen chloride at 0°. Next day, the mixture was refluxed for 1 hour, evaporated to 10 c.c., and crystallised. The *ester* crystallised from methyl alcohol in long, pale yellow needles, m. p. 197° (0·4 g.; 73·4%) (Found: C, 54·0; H, 4·2; N, 14·1. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%), insoluble in cold aqueous alkalis or mineral acids.

Sodium Hydrogen 3-(2′ : 4′-Dinitrophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate (II).—(*a*) A solution of sodium 1-(2′ : 4′-dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate in sodium hydroxide, prepared as described under (I) (p. 832), instead of being acidified after 25 minutes, was kept ice-cold for 6 days and then acidified. After removal of 2′ : 4′-dinitrobenzeneazo-β-naphthol (8·4 g.; 26%), the sodium hydrogen *salt* was isolated in the usual manner. It crystallised from hot water in bright yellow prisms, m. p. 230° (decomp.) (38 g.; 71·7%) (Found: S, 5·9; H_2O, 12·9. $C_{18}H_{11}O_9N_6SNa,4H_2O$ requires S, 6·0; H_2O, 13·6%). It is a yellow acid dye fugitive to light.

(*b*) Sodium benzaldehyde 2′ : 4′-dinitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid (4 g.), dissolved in sodium hydroxide (6 g.) and water (100 c.c.), was kept ice-cold for 6 days, then acidified with hydrochloric acid; yellow needles crystallised (3·6 g.; 90%). If the sodium hydroxide solution was kept at room temperature, the product was a black tar (2 g.) which, however, was convertible into 1-hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid by hydrolysis.

Action of Sodium Hydroxide on Sodium 1-(2′ : 4′-Dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate.—Sodium 1-(2′ : 4′-dinitrobenzeneazo)-β-naphthaquinone-1-sulphonate (212 g. in 2700 c.c. of water containing 150 g. of sodium carbonate), prepared as above, was poured into an aqueous solution (500 c.c.) of sodium hydroxide (125 g.) and measured quantities (200 c.c.) removed after various intervals of time. The aliquots were immediately acidified, boiled, and filtered from 2′ : 4′-dinitrobenzeneazo-β-naphthol, and the resulting solution of the sodium sulphonates was hydrolysed by boiling 10% hydrochloric acid into a mixture of (III) and (V), the percentage of (III) being determined from the amount of (IV) formed by refluxing with acetic anhydride and pyridine for 1 minute. The percentages of the compounds isolated are tabulated below.

Time of reaction with sodium hydroxide.	2′ : 4′-Dinitrobenzeneazo-β-naphthol.	2-(2′ : 4′-Dinitrophenylamino)*iso*indolinone-3-acetic acid.	1-Hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid.
17 seconds	49·8	30·2	—
5 minutes	44·6	35·4	—
15 minutes	40·7	39·3	—
30 minutes	37·2	42·8	—
1 hour	35·6	42·2	2·2
2 hours	30·9	43·4	5·7
4 hours	31·1	39·5	9·4
6 hours	31·3	35·2	13·5
8 hours	31·0	31·9	17·1
24 hours	31·4	15·4	33·2
48 hours	31·0	3·3	45·7

1-Hydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine-4-acetic Acid. (V).—A solution of (II) (5 g.) in water (200 c.c.) was boiled, and concentrated hydrochloric acid (20 c.c.) added during 2 hours. Boiling was continued until evolution of sulphur dioxide had ceased (10—12 hours) and the product had separated as an orange-brown precipitate. The *acid* crystallised from ethyl acetate in orange-yellow needles, m. p. 236° (2·9 g.; 83·1%) (Found: C, 51·4; H, 3·2; N, 15·2. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·3; N, 15·05%). It dissolves in aqueous sodium carbonate and hydroxide with yellowish-brown and deep crimson colours, respectively. Refluxing with acetic anhydride and pyridine for 20 hours gives 2 : 5-diketo-3-(2′ : 4′-dinitrophenyl)*iso*indolinopyrazolidocoline (IV). The *methyl* ester, prepared by the methyl alcohol–hydrogen chloride method, crystallised from methyl alcohol in pale yellow leaflets, m. p. 154° (Found: C, 53·0; H, 3·65; N, 14·4. $C_{17}H_{14}O_7N_4$ requires C, 52·8; H, 3·65; N, 14·5%). The *ethyl* ester crystallised from ethyl alcohol in light yellow plates, m. p. 150° (Found: C, 54·1; H, 4·1; N, 13·8. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%). The *anilide* crystallised from glacial acetic acid in yellow prismatic needles, m. p. 277° (Found: N, 15·55. $C_{22}H_{17}O_6N_5$ requires N, 15·65%).

1-Keto-3-(2′ : 4′-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetic Acid.—(*a*) Compound (V) (2 g.) was dissolved in water (4 c.c.), methyl alcohol (24 c.c.), and potassium hydroxide (4 g.), and methyl sulphate (3 c.c.) was added to the boiling deep purple solution during 15 minutes. After refluxing for a further 15 minutes, the solution was cooled and just acidified with hydrochloric acid, and the precipitate collected and macerated with sodium carbonate. Acidification of the extract gave 1-keto-3-(2′ : 4′-di-

nitrophenyl)-2-methyltetrahydrophthalazine-4-acetic acid (0·2 g.; 9·6%), whilst the insoluble residue was the methyl ester (1·5 g.; 69·6%). (*b*) Methyl 1-keto-3-(2′ : 4′-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetate was hydrolysed by warm sodium carbonate for 5 minutes. *1-Keto-3-(2′ : 4′-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetic acid* crystallised from methyl alcohol in light yellow prisms, m. p. 278° (Found: C, 53·1; H, 3·9; N, 14·3. $C_{17}H_{14}O_7N_4$ requires C, 52·8; H, 3·6; N, 14·4%). The *methyl* ester, prepared as described under (*a*) above, was also obtained by methylating 1-keto-3-(2′ : 4′-dinitrophenyl)-2-methyltetrahydrophthalazine-4-acetic acid, or by dissolving methyl 1-keto-3-(2′-nitrophenyl)-2-methyltetrahydrophthalazine-4-acetate (1 g.) in fuming nitric acid (*d* 1·5; 5 c.c.) at room temperature and pouring on ice (25 g.) after 5 minutes (1·1 g.; 97·5%). It crystallised from methyl alcohol in orange-yellow prisms, m. p. 167° (Found: C, 54·0; H, 4·1; N, 14·3. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%).

1-Hydroxy-3-(2′ : 4′-diaminophenyl)-3 : 4-dihydrophthalazine-4-acetic Acid Lactam (VI).—Compound (V) (20 g.) was added quickly to a boiling solution of stannous chloride (100 g.) in concentrated hydrochloric acid (250 c.c.). After the vigorous reaction had ceased, boiling was continued for 10 minutes, concentrated hydrochloric acid (250 c.c.) added, and the solution left to crystallise. The brownish-yellow crystals were dissolved in water, tin was removed by hydrogen sulphide, the filtrate boiled, and the hydrochloride of the lactam filtered off. It was basified with boiling, very dilute alkali, and the resultant yellow needles were washed with water, alcohol, and ether. The *lactam*, yellow needles, m. p. 290° (6·5 g.; 41·1%) (Found: C, 65·1; H, 4·7; N, 18·8. $C_{16}H_{14}O_3N_4$ requires C, 65·3; H, 4·8; N, 19·0%), is insoluble in water, organic solvents, and aqueous alkalis, but with concentrated mineral acids forms colourless water-soluble salts which diazotise readily and couple with β-naphthol to form a red dye. The *monoacetyl* derivative, obtained with acetic anhydride and a little pyridine, crystallised from aqueous alcohol in colourless plates, m. p. 306° (Found: C, 64·15; H, 4·8; N, 16·7. $C_{18}H_{16}O_3N_4$ requires C, 64·3; H, 4·8; N, 16·7%).

Action of Nitric Acid on 1-Hydroxy-3-(2′-aminophenyl)-3 : 4-dihydrophthalazine-4-acetic Acid Lactam.—The lactam (1 g.) was added during 1 minute to fuming nitric acid (*d* 1·5; 10 c.c.) at room temperature, and after 5 minutes the mixture was poured on ice (50 g.) and left to crystallise. On warming the yellow crystals with aqueous ammonia and crystallising from aqueous acetic acid, almost colourless prisms of 2′-amino-3-phenylphthalaz-1-one-4-acetic acid lactam, m. p. 298° (*J.*, 1935, 1807), were obtained. A similar experiment with 1-hydroxy-3-(2′ : 4′-diaminophenyl)-3 : 4-dihydrophthalazine-4-acetic acid lactam was unsuccessful.

1 : 4-Dihydroxy-3-(2′ : 4′-diaminophenyl)-3 : 4-dihydrophthalazine Dihydrate (VII).—Compound (VI) (2 g.) was macerated with concentrated sulphuric acid (20 c.c.) and the white paste was dissolved in water (24 c.c.). The clear red solution was refluxed for 2 hours, cooled, poured on ice (100 g.), and nearly neutralised with sodium carbonate. The pale yellow solid, which separated, crystallised from methyl alcohol in yellow, prismatic needles, m. p. 151° (1·3 g.; 62·4%) (Found: C, 55·0; H, 5·6; N, 18·5. $C_{14}H_{16}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%). It is slightly soluble in cold water with an orange colour, deepened by the addition of alkali, soluble in dilute mineral acids, and diazotises and couples with β-naphthol to form a red dye. Attempted reduction to *p*-amino-*o*-benzylenebenziminazole was unsuccessful.

1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (VIII).—(*a*) Compound (V) (5 g.) was macerated with concentrated sulphuric acid (50 c.c.) and water (60 c.c.), the fine suspension refluxed for 6 hours (a solution was obtained after 2 hours), cooled, and poured on ice (200 g.), and the yellow precipitate ground with aqueous sodium carbonate. Acidification of the extract and crystallisation of the precipitate from acetic acid gave light yellow needles of 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid, m. p. and mixed m. p. 270° (4 g.; 80%). The sodium carbonate-insoluble residue was 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (0·3 g.; 6·8%).

(*b*) Compound (V) (5 g.) was dissolved in boiling acetic acid (50 c.c.), and concentrated sulphuric acid (25 c.c.) was added. Boiling was continued for 10 minutes, the solution then poured into water (400 c.c.) and the precipitate rapidly filtered off; the filtrate slowly deposited brownish-yellow crystals. The two precipitates were combined and extracted with aqueous sodium carbonate. The alkali-soluble portion was 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid (2·9 g.; 58%) and the alkali-insoluble compound was 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (1·45 g.; 34·5%). The percentage yields of the two compounds isolated under various conditions are tabulated below.

Wt. of (V) (g.).	Vol. of acetic acid (c.c.).	Vol. of sulphuric acid (c.c.).	Final temp. of solution.	Vol. of water (c.c.).	*a* (%).	*b* (%).
2	20	2	128°	150	98·5	—
2	20	6	131	250	75·0	22·5
2	20	10	138	250	58·0	34·5
2	20	16	165	250	50·2	29·3
2	20	20	175	300	50·5	29·0
2	20	40	185	350	50·5	29·0
2	2	20	200	300	15·0	19·5

a, 2-(2′ : 4′-Dinitrophenylamino)*iso*indolinone-3-acetic acid.
b, 1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine.

(*c*) Compound (V) (2 g.) was heated with concentrated sulphuric acid (20 c.c.) at 180° for 3 minutes, and the solution was cooled and poured on ice (50 g.). The precipitate was a mixture of 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid (0·47 g.; 23·5%) and 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine (0·4 g.; 28·2%). Longer heating (15—20 minutes) with sulphuric acid converted the 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine into 2′ : 4′-dinitro-3-phenylphthalaz-4-one (see p. 835).

1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* crystallised from methyl alcohol or benzene–pyridine in light yellow prisms, m. p. 223° (Found : C, 50·8; H, 3·2; N, 17·0. $C_{14}H_{10}O_6N_4$ requires C, 50·9; H, 3·0; N, 17·0%). Attempts to dehydrate the compound with phosphorus trichloride in toluene, acetic anhydride, and pyridine, or cold concentrated sulphuric, acid failed, whilst concentrated sulphuric acid at 180° caused isomerisation to 2′ : 4′-dinitro-3-phenylphthalaz-4-one to occur simultaneously with dehydration (see below).

Nitro-3-arylphthalaz-1-ones. The reaction described under (*b*) above was attempted with other 1-hydroxy-3-(nitroaryl)-3 : 4-dihydrophthalazine-4-acetic acids, the general procedure being to add concentrated sulphuric acid (25 c.c.) to a boiling solution of the nitro-acid (5 g.) in glacial acetic acid (50 c.c.), to continue boiling for 10 minutes, and then to pour the solution into water (400 c.c.). Where necessary, the solution was partly neutralised with sodium carbonate. The precipitate was collected and treated as usual.

R = 4′-*Nitrophenyl.* The product was a mixture of the unchanged compound (1 g.; 20%) and 4′-nitro-3-phenylphthalaz-1-one, m. p. and mixed m. p. 333° (3 g.; 73·5%).

R = 2′-*Bromo*-4′-*nitrophenyl.* The product was a mixture of the unchanged compound (1 g.; 20%) and 2′-bromo-4′-nitro-3-phenylphthalaz-1-one, which crystallised from ethyl acetate in light brown plates, m. p. 209° (not 197° as previously described; *J.*, 1935, 1136) (2·1 g.; 49·3%). Attempts to methylate this compound were unsuccessful.

R = 2′-*Chloro*-4′-*nitrophenyl.* The product was a mixture of the unchanged compound (0·8 g.; 16·1%) and 2′-chloro-4′-nitro-3-phenylphthalaz-1-one, which crystallised from alcohol in yellow needles, m. p. 196° (not 130—150° as previously described; *J.*, 1932, 17) (1·95 g.; 46·7%). Attempts to methylate this compound were unsuccessful.

R = 4′-*Chloro*-2′-*nitrophenyl.* The immediate precipitate on pouring the solution into water was the unchanged compound (1·05 g.; 21%), whilst the subsequent crystalline precipitate was a mixture of 2-(4′-chloro-2′-nitrophenylamino)*iso*indolinone-3-acetic acid, m. p. and mixed m. p. 278° (0·3 g.; 6%), and 4′-chloro-2′-nitro-3-phenylphthalaz-1-one, which crystallised from methyl alcohol in long, yellow, prismatic needles, m. p. 263° (not 233° as previously described; *J.*, 1935, 1806) (2 g.; 47·9%) (Found : C, 55·8; H, 2·8; N, 14·0; Cl, 11·4. Calc. for $C_{14}H_8O_4N_3Cl$: C, 55·7; H, 2·65; N, 13·9; Cl, 11·7%). The *picrate* crystallised from methyl alcohol in pale yellow, prismatic needles, m. p. 230° (Found : C, 45·1; H, 2·4; N, 15·7. $C_{20}H_{11}O_{10}N_6Cl$ requires C, 45·2; H, 2·1; N, 15·8%).

Action of Methyl Sulphate on 1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* (VIII).—Compound (VIII) (0·55 g.) dissolved in nitrobenzene (12 c.c.) at 110° was treated with methyl sulphate (1 g.) for 1·5 hours. Nitrobenzene was removed by distillation with steam, and the residue cooled and basified. The yellow powder, m. p. 149—153°, was crystallised from either methyl or ethyl alcohol with formation of the corresponding ether. 1 : 4-*Dimethoxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* crystallised in lustrous yellow plates, m. p. 196° (Found : C, 53·8; H, 3·95; N, 16·0. $C_{16}H_{14}O_6N_4$ requires C, 53·65; H, 3·9; N, 15·7%). 1-*Methoxy*-4-*ethoxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* crystallised in lustrous yellow plates, m. p. 197° (Found : C, 55·0; H, 4·1; N, 15·0. $C_{17}H_{16}O_6N_4$ requires C, 54·85; H, 4·3; N, 15·05%). Heating first at 110° and then at 140° for 2 hours merely gives an intractable resin and no 4-keto-1-methoxy-3-(2′ : 4′-dinitrophenyl)-3 : 4-dihydrophthalazine is formed.

Action of Chromium Trioxide on 1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* (VIII).—Compound (VIII) (2 g.), dissolved in acetic acid (100 c.c.) at 40°, was treated with chromium trioxide (1·2 g.) with vigorous stirring. After 10 minutes, the deep green solution was poured on ice (250 g.); the yellow precipitate crystallised from acetic acid in pale yellow needles, m. p. 271°, identical with a specimen of synthetic phthalyl-2′ : 4′-dinitrophenylhydrazide (see p. 837), m. p. and mixed m. p. 271° (1·6 g.; 80·5%). Under identical conditions, nitro-3-arylphthalaz-1-ones (R = 3′- or 4′-nitro-, or 4′-chloro-2′-nitrophenyl) were unaffected, and even at 100° were recovered unchanged.

2′ : 4′-*Dinitro*-3-*phenylphthalaz*-4-*one.*—*o*-Phthalaldehydic acid (1·5 g.) dissolved in boiling alcohol (25 c.c.) was slowly poured into a boiling solution of 2 : 4-dinitrophenylhydrazine (2 g.) in alcohol (300 c.c.). After 5—10 minutes' refluxing, the red, flocculent precipitate of *o-carboxybenzaldehyde*-2′ : 4′-*dinitrophenylhydrazone* was crystallised from alcohol; light red, hair-like needles, m. p. 270° after becoming yellow at about 240° (3·2 g.; 96·1%) (Found : C, 50·6; H, 3·1; N, 16·7. $C_{14}H_{10}O_6N_4$ requires C, 50·9; H, 3·0; N, 17·0%). Ring closure was effected only by heating with concentrated sulphuric acid to 180° for 2—3 minutes and then diluting with ice (95% conversion). 2′ : 4′-*Dinitro*-3-*phenylphthalaz*-4-*one* crystallised from methyl alcohol or benzene in green-tinged prisms, m. p. 238° (Found : C, 54·0; H, 2·6; N, 17·8. $C_{14}H_8O_6N_4$ requires C, 53·85; H, 2·6; N, 17·95%). It does not form salts with mineral acids and does not form a picrate or perchlorate. Attempts to prepare it by nitrating the corresponding 4′- or 2′-nitro-compound with fuming nitric acid (*d* 1·5) alone or mixed with concentrated sulphuric acid at 80° failed, the material remaining unaltered.

Conversion of 1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine* (VIII) *into* 2′ : 4′-*Dinitro*-3-*phenylphthalaz*-4-*one.*—(*a*) Compound (VIII) (4 g.) was heated with concentrated sulphuric acid (20 c.c.) at 180° for 5 minutes, the solution cooled and poured on ice (50 g.), and the colourless precipitate well washed with aqueous sodium carbonate; it crystallised from methyl alcohol in green-tinged prisms, m. p. 238° (1·1 g.; 26·0%).

When (V) was heated similarly with sulphuric acid for 20 minutes, the product was a mixture of 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid (III) (0·94 g.; 23·5%) and 2′ : 4′-dinitro-3-phenylphthalaz-4-one (0·47 g.; 13·4%).

(*b*) (i) Compound (VIII) (0·75 g.) heated with aqueous hydrochloric acid (1 : 17; 18 c.c.) at 155° for 6 hours was unchanged. (ii) Compound (VIII) (0·75 g.) heated with aqueous hydrochloric acid (2 : 16; 18 c.c.) at 190° for 6 hours gave a mixture of red needles and orange-yellow prisms, which were separated by aqueous sodium carbonate in which the former were soluble. The alkali-insoluble compound was 2′ : 4′-dinitro-3-phenylphthalaz-4-one (0·35 g.; 42·9%), but the alkali-soluble compound (0·5 g.) was not analogous to any derivative previously obtained. The latter was precipitated by acid; it crystallised from alcohols in red needles, m. p. 270—286°, but the inconsistent analytical results could not be

interpreted. It was clearly an intermediate stage in the formation of 2′ : 4′-dinitro-3-phenylphthalaz-4-one, however, because it yielded that compound in green-tinged prisms, m. p. 238°, when crystallised from toluene or treated with dehydrating agents.

1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine* (IX).—(*a*) Oxidation of (V) with potassium dichromate in aqueous sulphuric acid always gave a mixture of (III) and 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine (IX) readily separable by extracting the former with aqueous sodium carbonate, the relative proportion of the two formed depending on the dilution of the sulphuric acid. Compound (V) (10 g.) was dissolved in concentrated sulphuric acid (75 c.c.), and the solution diluted with ice (100 g.) and stirred for 3 hours, potassium dichromate (5 g.) being added in portions during the first hour. After a time, the precipitate was filtered off and added to the further precipitate obtained by partial neutralisation of the filtrate. The percentage yields of compounds (III) and (IX) isolated under various conditions are tabulated below.

Wt. of (V) (g.).	Vol. of sulphuric acid (c.c.).	Wt. of ice added (g.).	*a* (%).	*b* (%).
10	75	50	98	—
10	75	100	65	16·2
10	75	150	50	40·5
10	75	200	50 *	38·9

a, 2-(2′ : 4′-Dinitrophenylamino)*iso*indolinone-3-acetic acid.

b, 1 : 4-Dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine.

* In this experiment, the alkali-soluble portion was a mixture of unchanged (V) and (III), separable by fractional crystallisation from ethyl acetate.

(*b*) Compound (V) (2 g.) was dissolved in fuming nitric acid (*d* 1·5; 12·5 c.c.). The reaction was vigorous and, after 10 minutes at room temperature, the solution was poured on ice (50 g.) and the yellow precipitate macerated with aqueous sodium carbonate to extract (III) (0·45 g.; 22·5%) from (IX) (0·65 g.; 35·1%). No nitrate of 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine was obtained (see 4′-nitro-3-phenylphthalaz-4-methyl-1-one nitrate below).

1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine* crystallised from benzene–pyridine or methyl alcohol in orange prisms, m. p. 232° (Found : C, 52·4; H, 3·7; N, 16·1. $C_{15}H_{12}O_6N_4$ requires C, 52·3; H, 3·5; N, 16·3%). Attempts to methylate this compound with methyl sulphate failed, as did also attempts to dehydrate it by means of phosphorus trichloride in toluene, acetic anhydride, and pyridine, or cold concentrated sulphuric acid. The action of hot concentrated sulphuric acid is described below.

When (IX) is crystallised from methyl alcohol containing a trace of mineral acid, however, 1-*hydroxy*-4-*methoxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine*, light orange, prismatic needles, m. p. 185°, is obtained (Found : C, 53·55; H, 4·1; N, 15·6. $C_{16}H_{14}O_6N_4$ requires C, 53·65; H, 3·9; N, 15·7%), reconverted into 1 : 4-dihydroxy-3-(2′ : 4′-dinitrophenyl)-4-methyl-3 : 4-dihydrophthalazine by boiling with ammonia (*d* 0·88) for 5 minutes.

4′-*Nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one Nitrate*.—(*a*) 1-Hydroxy-3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (2 g.) was treated with fuming nitric acid (*d* 1·5; 12·5 c.c.). The reaction was vigorous. After 10 minutes, the mixture was poured on ice (50 g.) and the precipitate macerated with aqueous sodium carbonate. The alkali-soluble portion was unchanged 1-hydroxy-3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (0·3 g.; 15%), whilst the insoluble compound was 4′-nitro-3-phenyl-4-methylphthalaz-1-one nitrate (1·23 g.; 60·0%). (*b*) 4′-Nitro-3-phenyl-4-methylphthalaz-1-one (Rowe, Levin, and Peters, *J.*, 1931, 1070) (1 g.) was treated similarly and the *nitrate* was obtained (1·1 g.; 90·1%). It crystallised from methyl alcohol in brown needles, m. p. 169° (Found : C, 52·3; H, 3·5; N, 16·3. $C_{15}H_{12}O_6N_4$ requires C, 52·3; H, 3·5; N, 16·3%), reconverted into the base by boiling with concentrated ammonia.

Action of Chromium Trioxide on 1 : 4-*Dihydroxy*-3-(2′ : 4′-*dinitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine*.—Compound (IX) (1 g.), dissolved in acetic acid (65 c.c.) at 40°, was treated with chromium trioxide (0·5 g.) with vigorous stirring. After 10 minutes, the green solution was poured on ice (100 g.), and the yellow precipitate filtered off, washed well with aqueous sodium carbonate and crystallised from acetic acid; pale yellow prismatic needles, m. p. 271°, identical with a specimen of synthetic phthalyl-2′ : 4′-dinitrophenylhydrazide (see p. 837), m. p. and mixed m. p. 271° (0·5 g.; 55·1%). Under identical conditions, nitro-3-phenyl-4-methylphthalaz-1-ones (R = 2′-, 3′- or 4′-nitrophenyl) were unaffected, and even at 100° were recovered unchanged.

2′ : 4′-*Dinitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*.—(*a*) Equimolecular proportions of acetophenone-*o*-carboxylic acid (*J.*, 1936, 312; 1928, 2555) and 2 : 4-dinitrophenylhydrazine (2 g.) were condensed. *o*-*Carboxyacetophenone* 2′ : 4′-*dinitrophenylhydrazone* crystallised from methyl alcohol in orange-red needles, m. p. 200° (3·34 g.; 96·1%) (Found : N, 16·3. $C_{15}H_{12}O_6N_4$ requires N, 16·3%). Ring closure was effected only by heating it (1 g.) with concentrated sulphuric acid (10 c.c.) at 180° for 2—3 minutes and then pouring on ice (0·8 g.; 84·5%). (*b*) Compound (V) (4 g.) was heated with fuming hydrochloric acid (*d* 1·19; 8 c.c.) at 180° for 2 hours. The solid was filtered off and ground successively with warm aqueous ammonia and 10% aqueous sodium carbonate. The alkali-soluble portion was (III) (0·1 g.; 2·5%), whilst the alkali-insoluble compound was 2′ : 4′-dinitro-3-phenyl-1-methylphthalaz-4-one (2·3 g.; 65·6%). (*c*) A solution of (IX) (2 g.) in concentrated sulphuric acid (10 c.c.) was heated to 180° for 3 minutes, cooled, and poured on ice (1 g.; 52·7%). (*d*) Compound (X) (0·5 g.) was heated with concentrated sulphuric acid (5 c.c.) at 180—185° for 3 minutes, cooled, and poured on ice (0·4 g.; 80%). 2′ : 4′-*Dinitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* crystallised from benzene in almost colourless needles, m. p. 248° (Found : C, 55·1; H, 2·85; N, 17·1. $C_{15}H_{10}O_5N_4$ requires C, 55·2; H, 3·05; N, 17·2%). It does not form salts with mineral acids, does not form a picrate or perchlorate, and is unaffected by heating with aqueous hydrochloric acid (1 : 8) in a sealed tube. Attempts to prepare it by nitrating the corresponding 4′- or 2′-nitro-compound failed, the material remaining unaltered.

2-(2′ : 4′-*Dinitrophenylamino*)-3-*methyleneisoindolinone* (X).—Compound (IX) (0·75 g.) was heated with aqueous hydrochloric acid (1 : 8; 18 c.c.) at 190° for 6 hours (no action occurred at 150°), and the product ground with dilute hydrochloric acid and washed well with aqueous sodium carbonate. The *isoindolinone* crystallised from methyl alcohol in pale greenish-yellow needles, m. p. 198° (0·4 g.; 56·3%) (Found: C, 55·3; H, 2·95; N, 17·1. $C_{15}H_{10}O_5N_4$ requires C, 55·2; H, 3·05; N, 17·2%). Heating this compound with sulphuric acid at 180° converted it into 2′ : 4′-dinitro-3-phenyl-1-methylphthalaz-4-one, whilst refluxing it (1 g.) with alcoholic sodium ethoxide (0·2 g. sodium in 25 c.c. of alcohol) for 30 minutes, pouring on ice, and acidifying with hydrochloric acid gave *o*-carboxyacetophenone 2′ : 4′-dinitrophenylhydrazone (0·9 g.; 85·3%), and oxidation of it (1 g.) in acetic acid (30 c.c.) at 40° with chromium trioxide (0·5 g.) and pouring on ice gave phthalyl-2′ : 4′-dinitrophenylhydrazide (0·66 g.; 65·8%).

Action of Potassium Permanganate on 1-*Hydroxy*-3-(2′ : 4′-*dinitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid.*—(*a*) Treatment of (V) (10 g.) suspended in water (100 c.c.) at 60° with potassium permanganate (15 g.) added slowly during 90 minutes, followed by dilution with water (500 c.c.), filtering from manganese dioxide, and acidifying with hydrochloric acid gave 2-(2′ : 4′-dinitrophenylamino)*iso*indolinone-3-acetic acid, m. p. and mixed m. p. 270° (4·8 g.; 48%).

(*b*) Treatment of (V) (10 g.) suspended in water (50 c.c.) at 80° with potassium permanganate (15 g.) added all at once, and isolation of the product as described under (*a*) above, gave a brownish precipitate of 1 : 4-*diketo*-3-(2′ : 4′-*dinitrophenyl*)*tetrahydrophthalazine*, which crystallised from acetic acid in brownish-yellow prisms, m. p. 271° (1·5 g.; 17·0%) (Found: C, 51·2; H, 2·9; N, 16·8. $C_{14}H_8O_6N_4$ requires C, 51·2; H, 2·5; N, 17·1%).

o-*Carboxybenzo*-2′ : 4′-*dinitrophenylhydrazide.*—2 : 4-Dinitrophenylhydrazine (2 g.) was condensed with phthalic anhydride (1·5 g.) in chloroform (600 c.c.). The *carboxy-hydrazide* crystallised from chloroform in pale yellow, prismatic needles, m. p. 227°, resolidifying and melting at 270° (3 g.; 87·6%) (Found: C, 48·55; H, 3·05; N, 15·9. $C_{14}H_{10}O_7N_4$ requires C, 48·55; H, 2·9; N, 16·2%.

Phthalyl-2′ : 4′-*dinitrophenylhydrazide.*—(*a*) *o*-Carboxybenzo-2′ : 4′-dinitrophenylhydrazide (2 g.) was refluxed with acetic acid (15 c.c.) for 1 hour (1·7 g.; 89·7%). (*b*) The *hydrazide* was also obtained by the oxidation of (VIII), (IX), or (X) with chromium trioxide in acetic acid. It crystallised from acetic acid in pale yellow prismatic needles, m. p. 271° (Found: C, 51·1; H, 2·4; N, 17·2. $C_{14}H_8O_6N_4$ requires C, 51·2; H, 2·5; N, 17·1%). It dissolved on warming in alcoholic sodium hydroxide with a deep reddish-brown colour, and the solution after being refluxed for 18 hours gave some *o*-carboxybenzo-2′ : 4′-dinitrophenylhydrazide but no 1 : 4-diketo-3-(2′ : 4′-dinitrophenyl)tetrahydrophthalazine.

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

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[*Received, September 12th,* 1946.]

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163. *The Crystal Structure of Pentaerythritol Tetranitrate.*

By A. D. BOOTH and F. J. LLEWELLYN.

The crystalline structure of pentaerythritol tetranitrate has been completely elucidated by means of quantitative *X*-ray measurements utilising all those {*hkl*} diffracted beams obtainable with Cu-*K*α and Mo-*K*α radiations. The interatomic distances within the molecule are C–C = 1·50, C–O_1 = 1·37, O_1–N = 1·36, N–$O_{2,3}$ = 1·27 A. Two oxygens of the nitrate are equivalent; the third is at the normal single-bond distance from the nitrogen atom. An attempt is made to explain, in terms of resonance, the extraordinary shortness of the C–O bonding.

ALTHOUGH there are many data in the literature concerning the size and shape of the nitro-group, little evidence is available on these features of the nitrate group in organic substances. Admittedly, both fluorine nitrate and methyl nitrate (Pauling and Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 13) have been examined by electron-diffraction methods from which it has been deduced that the nitrate group is planar; however, probably because of the few compounds available, no determinations of the structure of any solid nitrates have previously been completed.

Pentaerythritol tetranitrate is ideally suited to such a study since the molecule is fairly simple and possesses high symmetry. In addition, it possesses explosive properties (it was used extensively during the war as a high explosive—P.E.T.N.) and therefore it is not unlikely that the molecule might exhibit anomalous bond lengths as evidence of this instability.

Two crystallographic examinations had been made; Knaggs (*Min. Mag.*, 1925, **20**, 346) found that pentaerythritol tetranitrate crystallises in the ditetragonal bipyramidal class exhibiting the forms {100} and {111}; axial ratios determined goniometrically are $a : c = 1·000 : 0·506$, refractive indices $\omega = 1·554$, $\epsilon = 1·553$, d 1·773 g./c.c., imperfect cleavage on (100). *X*-Ray single-crystal photographs obtained by using Co-*K*α radiation led to the cell dimensions $[a] = 13·2$ A., $[c] = 6·66$ A., and the space-group D_{4h}^{7}. An arrangement of the four molecules in the unit cell was deduced from about twelve qualitative intensity measurements. Later, Gerstacker, Möller, and Reis (*Z. Krist.*, 1927, **66**, 355) obtained large tetragonal crystals exhibiting the forms {110} and {101} by crystallisation from acetone, and *X*-ray single-crystal

rotation photographs and Laue photographs gave the cell dimensions $[a] = 9{\cdot}38$ A., $[c] = 6{\cdot}69$ A., and the space-group $V_d^4 = P\bar{4}2_1c$.

The unit cell reported by Knaggs is centred and contains four molecules; by means of an axial transformation such that $\frac{1}{2}[110]$ (Knaggs) becomes [100], a primitive cell with dimensions $[a] = 9{\cdot}33$ A., $[c] = 6{\cdot}66$ A. is obtained, in fair agreement with the dimensions reported by Gerstacker *et al.* Claringbull (private communication) has redetermined the unit cell and space-group by means of single-crystal rotation and oscillation photographs, using Cu-$K\alpha$ radiation, finding $[a] = 9{\cdot}38$ A., $[c] = 6{\cdot}70$ A., and D_{2d}^4 (V_d^4) $= P\bar{4}2_1c$, respectively.

Preliminary Crystallographic Data.—Well-defined crystals of pentaerythritol tetranitrate exhibiting the forms {110} and {101} were obtained by crystallisation from acetone. It is noteworthy that no modification in the method of crystallisation produced any other forms. *X*-Ray single-crystal photographs confirmed the cell dimensions found by Claringbull, and oscillation photographs revealed the halvings $\{hhl\}$ absent when $l \neq 2n$, $\{h00\}$ absent when $h \neq 2n$, $\{0k0\}$ absent when $k \neq 2n$, whence the space-group is $P\bar{4}2_1c$. The density is 1·773 g./c.c., the calculated value for two molecules in the unit cell being 1·78 g./c.c.

Whilst the crystal as a whole therefore possesses considerable symmetry, the probable accuracy of the structure determination is limited by the absence of a centre. Since the unit cell contains two molecules, the central carbon atom of each molecule must lie in a special position; that of the first molecule is located at the origin of the cell (0, 0, 0) and that of the second at the centre $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$. The four $\cdot CH_2 \cdot O \cdot NO_2$ groups of each molecule are inter-related by the four-fold alternating axis which passes through the central carbon atom. A determination of the parameters of one of the $\cdot CH_2 \cdot O \cdot NO_2$ groups is therefore sufficient to define the molecule located around the origin; the second molecule in the cell, surrounding the carbon atom at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$, is derived from the first by the glide planes of symmetry lying in the (110) planes. The complete structure is therefore defined by the parameters of the six atoms $C \cdot C \cdot O \cdot NO_2$ (neglecting the hydrogen atoms whose positions are not revealed directly by *X*-rays).

Intensity Measurements.—Single-crystal oscillation photographs were taken about the [*a*], [*c*], and [110] axes, using both Cu-$K\alpha$ and Mo-$K\alpha$ radiations. The relative intensities of the spots produced by the diffracted beams were estimated by means of standard intensity scales. After correction for angular velocity variations (Cox and Shaw, *Proc. Roy. Soc.*, 1929, *A*, **127**, 71) and polarisation effects by means of the relation $F = k\sqrt{IDp/L}$ (where D is the Cox and Shaw factor, p the polarisation factor, and L the Lorentz factor) these were incorporated in a table of relative structure amplitudes. It is of interest that the photographs obtained with Mo-$K\alpha$ radiation gave no additional diffracted beams, indicating that those planes with spacing less than 0·77 A. (the minimum observable with Cu-$K\alpha$ radiation) do not give rise to diffracted beams of observable magnitude. The structure amplitudes were rendered absolute by comparing the intensities of the orders of (110) (obtained by reflection from a large ground 110 face) with the fourth-order (400) reflection from the ground cleavage face of rock-salt. The effects of extinction were estimated by repeating this procedure after immersing the crystal in liquid air.

Determination of the Structure.—The unit cell contains two molecules, the central carbon atoms being located in the special positions (000) and $(\frac{1}{2}\frac{1}{2}\frac{1}{2})$; of the remaining atoms 8 carbon atoms are in the general positions $(x_1y_1z_1)$, $(\bar{y}_1x_1\bar{z}_1)$, $(\bar{x}_1\bar{y}_1z_1)$, $(y_1\bar{x}_1\bar{z}_1)$, $(\frac{1}{2}-x_1, \frac{1}{2}+y_1, \frac{1}{2}-z_1)$, $(\frac{1}{2}-y_1, \frac{1}{2}-x_1, \frac{1}{2}-z_1)$, $(\frac{1}{2}+x_1, \frac{1}{2}-y_1, \frac{1}{2}-z_1)$, $(\frac{1}{2}+y_1, \frac{1}{2}+x_1, \frac{1}{2}+z_1)$; the eight nitrogen atoms in general positions $(x_2y_2z_2)$, etc., and the three sets of eight oxygens at $(x_3y_3z_3)$, $(x_4y_4z_4)$, and $(x_5y_5z_5)$, etc., respectively. Fifteen parameters, *viz.*, $x_1y_1z_1$, $x_2y_2z_2$, $x_3y_3z_3$, $x_4y_4z_4$, $x_5y_5z_5$, are thus required to define the structure.

Preliminary efforts to elucidate the structure included the use of the Patterson–Harker synthesis (Harker, *J. Chem. Physics*, 1936, **4**, 381) which had proved so useful in determining the structure of pentaerythritol (Llewellyn, Cox, and Goodwin, *J.*, 1937, 887). Patterson (*Z. Krist.*, 1935, **90**, 517) showed that the function $P_{(uvw)}$, where

$$P_{(uvw)} = \frac{1}{V}\sum_{-\infty}^{+\infty}\sum\sum F^2_{(hkl)}\, e^{-2\pi i(hu/a + kv/b + lw/c)}$$

reaches a maximum at those co-ordinates which correspond with interatomic distances in the structure. Harker (*loc. cit.*) extended Patterson's work to include specifically in certain limited evaluations of $P_{(uvw)}$ those interatomic vector distances occasioned by the symmetry of the structure. Thus in pentaerythritol tetranitrate two similar atoms in opposite arms of the molecule having co-ordinates $(x_ry_rz_r)$ and $(\bar{x}_r\bar{y}_rz_r)$ should provide a maximum in the function $P_{(xy0)}$ at the point $2x_r2y_r$. If by chance two atoms, crystallographically dissimilar, have the

same z co-ordinate, then their vector distance will also appear. In the same way the function $P_{(x\frac{1}{2}z)}$ should exhibit maxima at $(\frac{1}{2} - 2x_r)$, $(\frac{1}{2} - 2z_r)$, these points representing the vector distance between two crystallographically similar atoms located at $(x_r y_r z_r)$ and $(\frac{1}{2} - x_r, \frac{1}{2} + y_r, \frac{1}{2} - z_r)$.

Both of the Harker–Patterson sections were computed, and when plotted to form a contour map resulted in a large number of somewhat diffuse maxima which could not be correlated satisfactorily with any reasonable atomic model of the pentaerythritol tetranitrate molecule. Further sections, chosen in order to locate particular atoms, were then evaluated. For example, the section at $z = 0{\cdot}13$ should show, near the origin, a maximum in $P_{xy0{\cdot}13}$ due to the C_0–C_1 separation. If it is assumed that the central carbon atom has a tetrahedral valency arrangement and that the bond length is approximately 1·51 A., then the co-ordinate of C_1 is 0·125 (fractional co-ordinates). Neither this section nor any of the half dozen others computed at various distances along the [c] axis gave any information of value in this structure determination. One reason for this failure of the method may be mentioned. Because of the relatively large number of atoms in the unit cell (as compared with pentaerythritol) the number of vector distances which satisfy, or approximately satisfy, the conditions imposed by restricting one of the variables in $P_{(xyz)}$ in addition to those necessitated by space-group symmetry is probably considerable. Consequently the genuine maxima which could be used in the structure determination are masked by an unknown number of fortuitous maxima.

Following this lengthy attempt to utilise the Patterson–Harker syntheses, attention was focused on the projection of the structure on to the c-plane. This projection possesses a centre of symmetry, so the calculation of structure factors for the planes $hk0$ is greatly simplified. Trial and error methods, using reasonable molecular models and molecular orientations, followed by structure-amplitude calculations from approximate (xy) co-ordinates, were not immediately successful; the method led eventually, however, to the correct solution when used in conjunction with the Bragg structure-amplitude charts (*Nature*, 1936, **138**, 362; see also Bragg and Lipson, *Z. Krist.*, 1936, **95**, 323). Following is an outline of the method which illustrates a new application for the structure-amplitude charts in which they prove to be at least as valuable as for the purpose for which they were proposed.

The structure amplitude of a plane ($hk0$) is obtained by summing one of the following functions over each crystallographically different atom in the unit cell:

$$F_{hk0} = \Sigma\ 4f(\cos 2\pi hx \,.\, \cos 2\pi ky + \cos 2\pi kx \,.\, \cos 2\pi hy) \qquad h + k = 2n$$

$$F_{hk0} = \Sigma\ 4f(\sin 2\pi hx \,.\, \sin 2\pi ky + \sin 2\pi kx \,.\, \sin 2\pi hy) \qquad h + k \neq 2n$$

where f is the atomic scattering factor of a particular kind of atom for the plane ($hk0$).

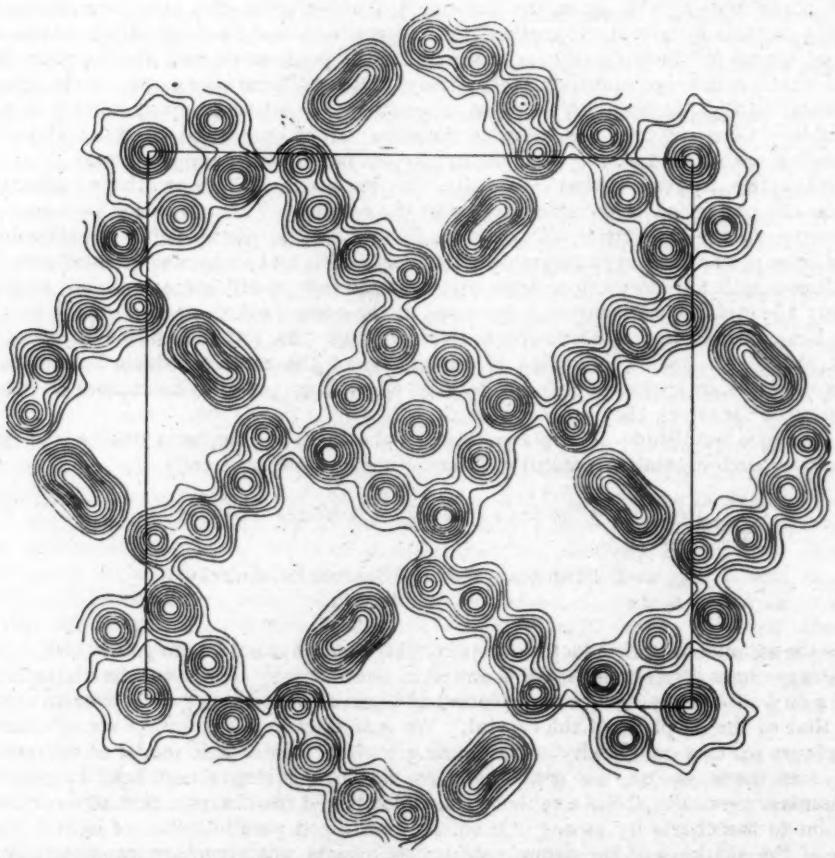
The Bragg chart for the plane $hk0$ is simply a contour map of one of the above functions, depending on $h + k$ being even or odd, plotted at intervals (assuming $f = 1$) over an area whose shape is that of the (c) plane of the crystal. We manufactured a complete set of charts of all the $hk0$ planes up to a complexity corresponding to 730. An atomic model of one arm of the molecule was made up on the same scale as the Bragg charts and held by means of a wall goniometer vertically above a table top on which rested the charts. A shadow of the model was cast on to the charts by means of a suitably arranged parallel beam of light. From the positions of the shadows of the atoms cast on the charts, the structure amplitude is readily obtained by summing the contribution of each atom. (In the preliminary work f_c was taken as unity, $f_N = 7/6$, and $f_0 = 8/6$; the structure amplitude being obtained by multiplying the sum of the contributions of the carbon atoms by unity, the sum of the nitrogen by 7/6, etc., and then the total of all the atoms by f_c.)

Reference to the table of absolute structure amplitudes shows that $F_{120} = 8{\cdot}5$, $F_{220} = 40{\cdot}7$, and $F_{440} = 35{\cdot}8$. The only molecular model and orientation which gives calculated values in approximate agreement with these observed amplitudes is one in which the arm of the molecule zigzags across the [a]. A little experimentation with a molecule of this sort led almost immediately to a set of (xy) co-ordinates which gave reasonable agreement between observed and calculated structure amplitudes up to $\xi = 1{\cdot}0$. A Fourier projection on the c-plane resulted in refinement of these co-ordinates and then, with the inclusion of the remaining $hk0$ planes, the contour map shown in Fig. 1 was produced; from this the xy co-ordinates are:

C_1	0·120	0·061	N	0·285	−0·016	O_3	0·360	0·102
O_1	0·162	−0·048	O_2	0·318	−0·106			

The actual model used in determining these co-ordinates tended continually upwards from the origin to the oxygens of the nitrate group; but it was immediately obvious from the (xy) co-ordinates that other values of the z co-ordinates were possible. Such co-ordinates were then calculated for the various molecular shapes using the following bond lengths: C_0–C_1 = 1·51, C_1–O_1 = 1·41, O_1–N = 1·36, N–$O_{2,3}$ = 1·24 A. The calculation of a few $\{hkl\}$ structure amplitudes soon showed that the original molecule was the correct one. Consequently, the structure amplitudes of all the $\{hkl\}$ planes up to $\xi = 1$ were calculated; fair agreement was obtained and, utilising the calculated phase angles, three-dimensional Fourier line syntheses parallel to the [c] axis and passing through the xy co-ordinates of the atoms were computed.

FIG. 1.



Two-dimensional Fourier projection on (001). *Contours are plotted at intervals of* 1 *electron per* A.^{2}, *the lowest being* 1 *electron per* A.^{2}.

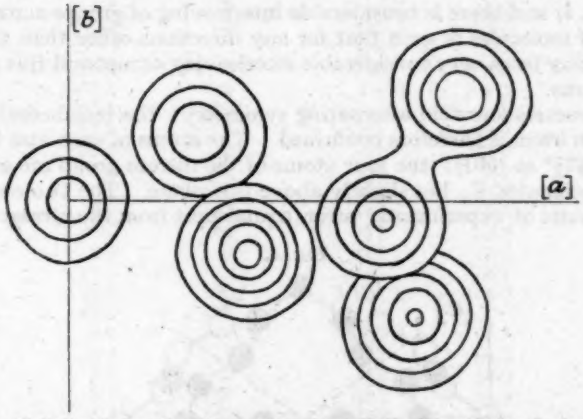
The structure was then refined by means of two complete sets of three-dimensional Fourier sections parallel to the c-plane and three-dimensional Fourier lines parallel to the [c] axis through each of the atoms. Fig. 2 is a composite drawing made from the final set of Fourier sections parallel to the c-plane.

The final atomic co-ordinates, and a list of the principal interatomic distances and bond angles, are given below:

Atom.	x.	y.	z.		
C_0	0·000	0·000	0·000	C_0–C_1 = 1·50 A.	C_1–C_0–C_1 = 112½°
C_1	0·119	0·059	0·124	C_1–O_1 = 1·37 A.	C_0–C_1–O_1 = 108°
O_1	0·162	−0·044	0·256	O_1–N = 1·36 A.	C_1–O_1–N = 116°
N.....	0·284	−0·015	0·359	O_2–N = 1·27 A.	O_1–N–O_2 = 116°
O_2	0·318	−0·104	0·494	O_3–N = 1·28 A.	O_1–N–O_3 = 121°
O_3	0·356	0·099	0·325		

It is estimated that the accuracy attained is such that the interatomic distances are ± 0·02 A. and the valency angles ± 4°. These limits are somewhat wider than those tolerated in centrosymmetric structures; however, it is not considered practicable to refine the structure

FIG. 2.

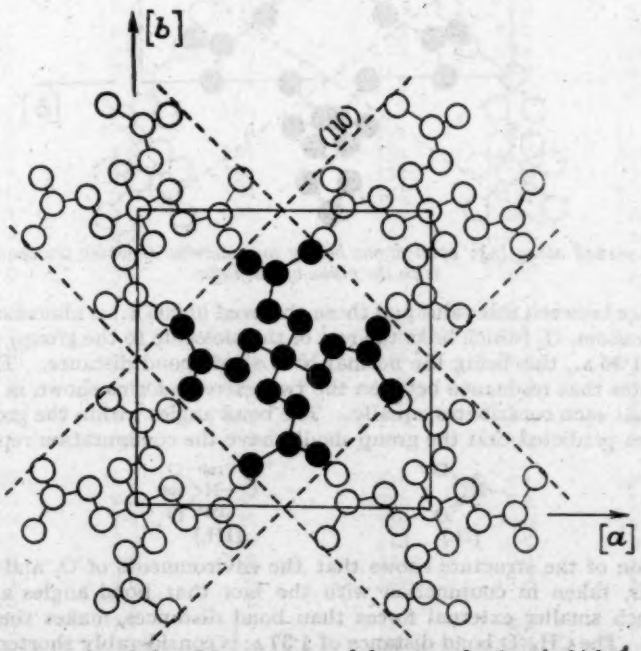


Contours are plotted at intervals of 2 electrons per A.^{3}, the lowest being 2 electrons per A.^{3}.

further with the present facilities for computation. The average discrepancy between the observed and the calculated structure amplitudes, neglecting 021 which is extinguished, is 22%.

Discussion of the Structure.—The molecular orientation viewed along the [*c*] axis is illustrated in Fig. 3; the open atoms belong to molecules of which the central carbon is in the plane of the

FIG. 3.



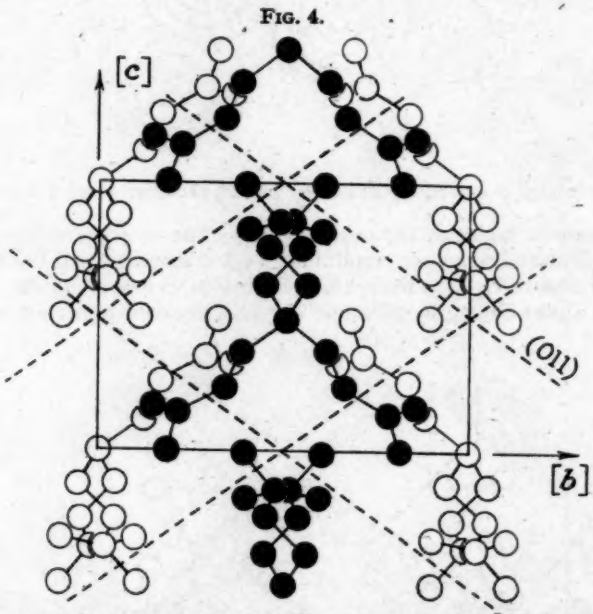
The structure viewed along [c]; *open atoms belong to molecules of which the centre carbon atom is in the plane of the paper.*

paper, and the black atoms are disposed about a central carbon atom located at ($\frac{1}{111}$). Fig. 4 represents the structure viewed along the [*a*] axis. The broken lines in both figures represent the traces of the naturally occurring faces (110) and (011), respectively. Since there is no

interleaving of groups across the trace of (110) (Fig. 3), cleavage is to be expected in this direction; this was first observed by Knaggs (*loc. cit.*) and we have confirmed it. The (110) face is populated almost entirely by nitrate groups, and it would appear from the separation of the oxygen atoms in neighbouring groups—3·2 A. and 3·4 A.—that the intermolecular forces approximate to the normal van der Waals. The structure viewed along the [*a*] axis is rather more confused (Fig. 4) and there is considerable interleaving of groups across the trace of (011). The arrangement of molecules is such that for any directions other than those represented by the naturally occurring faces very considerable interleaving occurs and this may account for the absence of other forms.

The molecule possesses four-fold alternating symmetry; the tetrahedral valency disposition of the central carbon atom is therefore confirmed. The atoms of each arm lie approximately in a plane inclined at 47½° to (001); the four atoms of the nitrate group are exactly coplanar and the carbon atom, designated C_1, lies slightly above this plane. The two oxygen atoms, O_2 and O_3 are, within the limits of experimental error, equidistant from the nitrogen atom at 1·275 A.;

FIG. 4.



The structure viewed along [a]; *open atoms belong to molecules of which the centre carbon atom is in the plane of the paper.*

the small difference between this value and those observed (0·005 A.) is almost certainly spurious. The third oxygen atom, O_1 (which links the rest of the molecule to the group), is separated from the nitrogen by 1·36 A., this being the normal N–O single-bond distance. The equivalence of O_2 and O_3 indicates that resonance between the two extreme forms shown in (I) and (II) must take place and that each contributes equally. The bond angles within the group are then as in (III). It has been predicted that the group should have the configuration represented by (IV),

but an examination of the structure shows that the environments of O_2 and O_3 are markedly different and this, taken in conjunction with the fact that bond angles are susceptible to distortion by much smaller external forces than bond distances, makes the observed values quite reasonable. The CH_2–O bond distance of 1·37 A: is considerably shorter than the normal single-bond separation. In pentaerythritol (Llewellyn, Cox and Goodwin, *loc. cit.*) this bond has a value of 1·46 A., and in pentaerythritol tetra-acetate (Goodwin and Hardy, *Proc. Roy. Soc.*, 1938, *A*, **164**, 369) it is 1·41 A. This shortening is undoubtedly significant and is related to the development of negative charges at the extremities of the arms of the molecule (*vide* the series pentaerythritol, pentaerythritol tetra-acetate, pentaerythritol tetranitrate).

Table of calculated and observed F values.

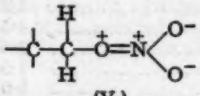
Plane.	F (obs.).	F (calc.).	α°.	Plane.	F (obs.).	F (calc.).	α°.
020	23·0	25·1	0	130	27·2	36·1	0
040	35·8	32·9	180	140	8·7	8·4	0
060	12·7	14·0	0	150	8·3	4·7	180
080	<2·5	1·0	0	160	13·2	13·4	0
0, 10, 0	<2·3	2·4	0	170	10·6	8·0	0
				180	4·3	2·3	0
011	5·8	10·4	0	190	8·9	8·8	180
021	40·4	83·5	0	1, 10, 0	8·7	4·1	0
031	29·0	26·5	180				
041	29·8	31·3	0	121	35·9	48·3	8
051	26·2	26·0	0	131	24·4	26·2	150
061	26·0	17·6	180	141	8·7	7·7	204
071	4·4	1·1	180	151	13·6	14·0	125
081	9·5	6·1	180	161	16·3	16·0	137
091	4·3	6·5	180	171	10·3	9·9	286
0, 10, 1	<2·5	2·8	0	181	17·4	16·7	58
				191	6·1	4·4	207
002	17·8	16·5	180	1, 10, 1	4·0	4·1	54
012	32·2	47·5	180				
022	9·8	8·0	180	112	15·4	14·1	156
032	15·7	21·4	0	122	30·7	34·7	349
042	9·4	3·3	0	132	20·0	21·7	348
052	8·0	2·8	180	142	14·5	14·3	161
062	4·2	5·4	180	152	12·9	14·0	245
072	7·0	8·4	180	162	14·6	12·3	184
082	4·9	1·5	0	172	8·6	8·3	282
092	11·3	12·7	180	182	9·6	7·9	209
0, 10, 2	11·1	9·2	0	192	9·5	9·1	346
				1, 10, 2	3·3	2·5	196
013	6·6	1·2	0				
023	2·4	1·6	180	123	13·2	15·8	239
033	19·6	16·0	0	133	17·7	19·3	227
043	7·0	5·0	180	143	7·1	10·1	138
053	18·3	17·5	0	153	9·8	8·5	65
063	11·1	13·9	0	163	11·3	6·4	307
073	3·9	3·8	0	173	17·3	18·0	352
083	2·7	0·9	0	183	5·5	7·1	320
				193	6·8	6·0	323
004	8·5	0·4	180				
014	13·9	20·1	0	114	8·4	11·3	289
024	3·1	3·6	180	124	14·7	20·0	9
034	3·8	4·0	180	134	5·3	7·8	290
044	8·5	6·9	180	144	10·6	11·8	38
054	4·3	2·3	180	154	14·6	14·1	24
064	7·8	8·4	0	164	5·9	2·6	351
074	3·5	1·9	0	174	4·2	5·7	60
084	4·5	6·7	180	184	3·7	3·5	231
015	10·0	7·9	180	125	8·5	9·1	59
025	7·4	7·7	180	135	9·8	12·3	106
035	6·7	0·4	180	145	10·4	10·2	57
045	<2·5	0·3	180	155	7·8	7·2	296
055	12·5	17·1	0	165	5·7	5·3	174
065	4·5	5·3	180	175	5·0	4·6	358
075	7·7	6·8	0	185	3·4	3·4	328
006	12·0	13·9	0	116	9·1	13·7	174
016	<3·0	0·3	180	126	2·8	1·0	233
026	7·5	1·8	180	136	10·0	14·0	7
036	4·8	1·1	180	146	10·7	9·7	242
046	3·9	5·9	180	156	2·8	1·5	100
056	7·1	4·6	0	166	3·6	1·7	88
066	<2·3	0·0	0				
076	3·4	2·7	0	127	8·5	8·1	353
				137	5·6	8·3	243
017	5·7	2·2	0	147	3·8	2·7	221
027	7·9	2·9	180				
037	6·3	5·5	180	220	40·7	52·1	180
047	4·0	4·4	180	230	21·5	23·5	0
				240	9·2	9·4	180
110	10·0	11·6	0	250	4·3	2·5	180
120	8·5	8·1	0	260	17·5	11·9	0

Plane.	F (obs.).	F (calc.).	α°.	Plane.	F (obs.).	F (calc.).	α°.
270	8·9	11·7	180	391	12·8	12·8	104
280	<2·8	1·6	180	3, 10, 1	3·8	3·9	350
290	6·3	7·9	0				
2, 10, 0	2·6	2·4	180	332	13·6	14·5	0
				342	19·9	22·4	143
231	9·1	6·7	145	352	3·6	8·6	292
241	7·1	6·4	19	362	3·9	1·6	99
251	13·6	11·8	66	372	6·8	5·3	159
261	18·8	20·1	208	382	6·6	7·7	333
271	5·9	3·3	43	392	3·5	4·1	60
281	3·6	2·6	256	3, 10, 2	4·2	3·1	193
291	10·4	9·8	336				
2, 10, 1	6·1	5·8	6	343	10·0	15·0	4
				353	7·9	12·7	113
222	30·5	44·6	297	363	3·7	3·1	354
232	28·4	37·2	137	373	6·2	6·4	6
242	21·4	25·1	330	383	6·0	5·0	233
252	8·2	2·7	126	393	2·7	2·5	245
262	5·3	10·0	87				
272	6·7	5·3	94	334	12·8	16·7	203
282	<2·8	0·9	151	344	3·5	6·8	297
292	3·6	2·9	312	354	5·1	6·2	60
2, 10, 2	3·7	1·0	6	364	10·0	9·2	351
				374	3·3	3·3	175
233	15·4	20·8	273	384	3·2	3·8	36
243	23·9	26·6	349				
253	8·9	9·6	233	245	11·8	11·9	22
263	4·4	4·5	92	355	5·4	7·1	293
273	7·6	5·0	279	365	4·0	7·3	21
283	11·0	12·6	202	375	3·0	3·5	34
293	3·5	3·5	222				
2, 10, 3	4·8	3·9	269	336	5·1	5·7	48
				346	4·6	6·1	174
224	19·7	20·6	73	356	2·9	4·4	180
234	3·9	5·3	272	366	2·8	4·8	16
244	7·7	7·0	6				
254	15·9	22·8	1	347	1·9	1·4	121
264	12·7	16·8	337				
274	4·6	7·4	350	440	24·8	27·5	0
284	3·5	0·2	214	450	8·9	8·0	180
294	4·4	2·9	5	460	12·3	8·4	0
				470	14·7	16·5	180
235	6·8	7·1	91	480	13·2	8·4	0
245	4·5	6·5	51	490	6·4	4·1	0
255	3·4	1·8	180	4, 10, 0	5·9	3·8	0
265	4·4	2·6	210				
275	7·6	7·8	86	451	7·5	6·9	220
285	3·8	3·8	75	461	14·2	14·0	119
				471	7·2	6·0	110
226	<2·9	2·2	116	481	8·2	8·0	72
236	8·8	6·2	280	491	8·1	8·2	350
246	5·0	6·2	20				
256	4·8	6·4	198	442	4·9	2·5	304
266	2·8	0·1	243	452	11·3	13·8	385
				462	8·4	8·5	134
237	3·9	1·7	138	472	7·0	7·7	106
247	4·0	2·8	3	482	7·5	7·8	315
257	3·4	2·9	34	492	1·7	0·7	311
				4, 10, 2	3·2	2·6	248
330	20·6	27·1	180				
340	12·4	11·8	180	453	11·2	12·4	92
350	11·9	19·2	180	463	11·1	13·1	23
360	3·6	5·3	0	473	8·3	10·8	15
370	17·4	17·2	0				
380	11·5	8·3	180	444	9·6	8·7	211
390	8·8	8·6	0	454	6·2	9·3	62
3, 10, 0	4·4	0·3	180	464	3·9	2·5	198
				474	8·8	10·3	193
341	22·6	22·0	290				
351	5·4	5·4	180	455	9·9	12·2	246
361	14·4	16·4	337	465	5·6	8·6	289
371	4·7	5·3	271	475	3·3	3·8	247
381	10·4	9·0	94				

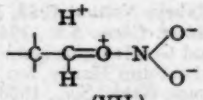
Plane.	F (obs.).	F (calc.).	α°.	Plane.	F (obs.).	F (calc.).	α°.
446	7·5	10·6	16	565	3·6	3·7	299
456	2·7	2·2	124				
				660	13·4	12·7	180
550	8·1	6·7	0	670	3·9	1·6	0
560	5·3	4·9	180	680	2·4	0·0	—
570	8·5	9·9	0	690	1·9	3·1	180
580	10·6	9·7	180				
590	8·5	8·0	180	671	5·5	6·7	91
				681	2·7	1·0	108
561	12·9	13·1	333	691	2·7	1·0	43
571	10·4	10·1	249				
581	5·3	3·3	11	662	10·9	5·9	88
591	3·2	2·9	88	672	11·1	10·9	50
				682	6·6	6·9	1
552	12·5	16·5	10				
562	6·2	7·6	10	673	6·6	5·9	349
572	5·6	6·2	101	683	5·6	2·5	100
582	10·6	10·0	18				
592	2·1	0·8	197	664	2·1	2·2	147
				674	4·0	4·2	298
563	10·7	10·5	124				
573	5·1	5·2	169	770	7·2	4·7	0
583	4·3	5·1	163	780	2·4	3·1	180
554	9·9	14·5	359				
564	4·0	1·3	167	781	5·7	4·3	116
574	4·3	3·3	231				
584	2·3	2·2	135	782	3·8	3·5	196

No entirely satisfactory explanation for the shortening of this C–O bond is forthcoming; an interpretation, which is attempted below, in terms of resonance leads to the existence of canonical forms which appear somewhat " exotic," and since the arguments are general, should apply also to other nitrates; the fact that the corresponding atomic separation in methyl nitrate (Pauling and Brockway, *loc. cit.*) is normal militates against the probability of the resonance explanation. However, for the moment this electron-diffraction evidence is laid aside because the authors cannot overlook the possibility that, since no abnormality of the sort was expected in methyl nitrate, a model incorporating a short C–O bond was probably not examined in much detail.

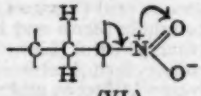
If one assumes that the negative charges on O_3 and O_3 and the resulting positive charge on the N produce a tendency for electrons in the remainder of the arm to drift towards the nitrogen, then two possible resonance forms (neglecting the resonance in the $\cdot NO_2$) may be considered,



(V.)

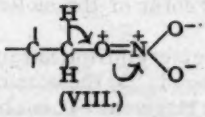


(VII.)

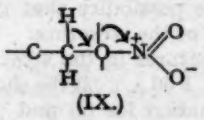


(VI.)

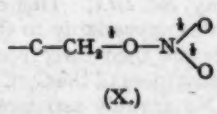
viz., (V), derived from the unexcited molecule by the electromeric shift (VI), and (VII), derived either from (V) by the shift (VIII) or from the unexcited molecule as in (IX).



(VIII.)



(IX.)



(X.)

Although it is recognised that both mechanisms are novel, these possibilities must be entertained if an explanation in terms of resonance is attempted.

Using the expression

$$B = (k_s x_s S + k_d x_d D)/(k_s x_s + k_d x_d)$$

(where B = length of the resonating bond, S = length of the single bond, x_s and x_d represent the extent of single- and double-bond character, respectively, and k_s and k_d are the force constants of single and double bonding), we can calculate x_s and x_d for all bonds in the structure. Such a calculation leads to a molecule (X), where the fractions represent the extent of double-bond character in the various bonds.

Four canonical forms of the molecule may therefore be postulated, *viz.*, (*a*)—(*d*). The

contributions of these forms are 1/3, 1/3, 1/6, and 1/6, respectively.

These simple calculations, in which it is recognised that no account is taken of the formal charges on the various atoms, lend support to the postulated resonance mechanism. Sutherland (private communication, to be published elsewhere) has observed the infra-red spectrum of pentaerythritol tetranitrate. He finds anomalies both in the nitrate group and in the CH_2 vibrations. The highest characteristic frequency of the NO_2 group (at 6 mμ) is abnormally high; this would indicate that the force constant for the N–O bond is higher than usually exists in nitro-paraffins, and consequently that this bond would be relatively shortened. These deductions are not in accordance with the crystallographic results, but it must be remembered that comparison is being made between the nitro-group of a nitro-paraffin and that of a nitrate. The CH_2 stretching vibrations are shown by Sutherland to be exceptionally weak, indicating that the charge distributions of the CH_2 group is considerably different from that of a CH_2 group in a paraffin chain. Unfortunately, no definite information could be obtained concerning the state of the C–O bond.

Whilst the infra-red work does not directly help in elucidating the structural riddle of the short C–O bond in pentaerythritol tetranitrate, it does lend support to the suggestion that the electronic configuration of the CH_2 grouping has been considerably modified. The resonance mechanism suggested earlier calls for a considerable alteration in the charge distribution on the CH_2 group, but whether such modification would result in a weaker band at 6·8 mμ is not certain.

The observation that the C_0–C_1 distance in pentaerythritol tetranitrate is 1·50 A.—considerably shorter than the value 1·54 A. found in diamond (Bragg and Bragg, *Proc. Roy. Soc.*, 1913, *A*, **89**, 277) and in the paraffins, ethane and *neo*pentane (Pauling and Brockway, *J. Amer. Chem. Soc.*, 1937, **59**, 1233)—is not inconsistent with this postulated modification of the CH_2 grouping. Similar values have been reported in a number of other organic compounds (see table below), so now it appears probable that the single-bond C–C separation in substances other than the paraffins and diamond approximate more nearly to 1·51 A. than to 1·54 A.

Carbon–Carbon Bond Lengths (A.) *in Various Organic Compounds.*

Succinic acid (Verweel and MacGillavry, *Nature*, 1938, **142**, 161)	1·52
Acetamide (Senti and Harker, *J. Amer. Chem. Soc.*, 1940, **62**, 2008)	1·51
Pentaerythritol (Llewellyn, Cox, and Goodwin, *loc. cit.*)	1·50
Pentaerythritol tetra-acetate (Goodwin and Hardy, *loc. cit.*)	1·52
Glycine (Albrecht and Corey, *J. Amer. Chem. Soc.*, 1939, **61**, 1087)	1·52
s-Bisnitroaminoethane (Llewellyn and Whitmore, unpublished)	1·52

The remaining bond distance within the molecule, O_1–N, is 1·36 A. in agreement with the normal single-bond separation reported in methyl nitrate and fluorine nitrate (Pauling and Brockway, *loc. cit.*). This excludes the possibility that the excited form of the molecule (V) contributes appreciably to the stability of the structure.

There are then three remarkable features in the structure of pentaerythritol tetranitrate: (1) The shortness of the C_0–C_1 bond, *viz.*, 1·50 A.; (2) the short C_1–O_1 bond; (3) the normal O_1–N bond. No entirely satisfactory explanation for (2) and (3) can yet be given. It is obviously necessary to examine in detail the structures of additional solid nitric acid esters in order to decide whether these bond lengths are peculiar to pentaerythritol tetranitrate or whether they are representative of these atomic separations in this type of compound.

One of the authors (A. D. B.) records his thanks to the Board of the British Rubber Producers' Research Association for the award of a Major Research Scholarship.

This work, which forms part of a programme of fundamental research sponsored by the Ministry of Supply at the University of Birmingham, was completed in February 1943; approval for publication has been granted by the Director General of Scientific Research and Development, Ministry of Supply.

THE UNIVERSITY, BIRMINGHAM 15. [*Received, September 6th*, 1946.]

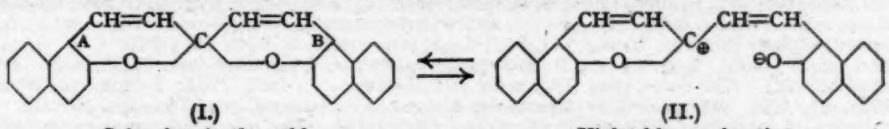
NOTES.

Experiments with Grignard Solutions. Part III. Action of Grignard Solutions on Thermochromic spiro-*Pyrans.* By ALEXANDER SCHÖNBERG, AHMED MUSTAFA, and (in part) (MISS) WAFIA ASKER.

A NUMBER of *spiro*pyrans, *e.g.*, (I), form colourless crystals which give colourless solutions in cold inert solvents, but develop an intense colour, *e.g.*, violet-blue, on heating (Dickinson and Heilbron, *J.*, 1927, 1699) and the process is reversible. This phenomenon has been studied chiefly by Heilbron, Löwenbein, Dilthey and their respective schools and they all agree that the colour change is due to ionic dissociation with the formation of a heteropolar molecule (II).

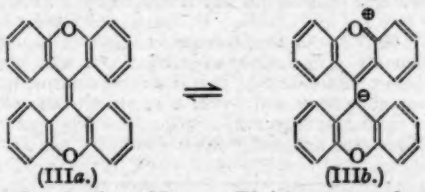
The *spiro*pyrans showing this colour phenomenon are well crystallised substances, stable to heat and to oxygen; nevertheless, but few physicochemical investigations of the colour phenomenon have been carried out, and the influence of substitution has not been investigated.

A possible approach to this phenomenon may be to apply the theories used to explain the stability of the free radicals of the triphenylmethyl type. It has been pointed out (see Gilman, "Organic Chemistry," 2nd edtn., p. 1979) that the free radicals formed by dissociation of hexaphenylethane are stabilised by resonance, and it seems possible that this theory may also explain the stability of the zwitterions such as (II). On the other hand, the lowered stability of the spirans (I) may be due to their non-planar configuration (see rings A and B) interfering with the development of resonance.



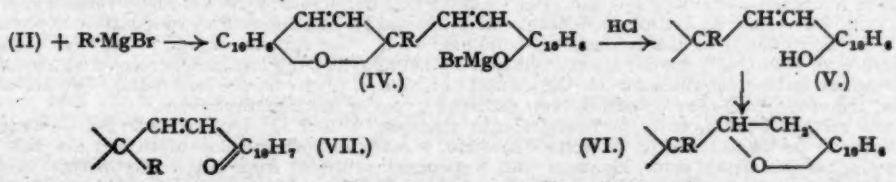
(I.) Colourless in the cold. (II.) Violet-blue on heating.

The thermochromic behaviour of the *spiro*pyrans may be related to that of certain ethylenes, *e.g.*, (III*a*) and (III*b*) (Schönberg, Abdel Fattah Ismail, and Asker, *J.*, 1946, 442).



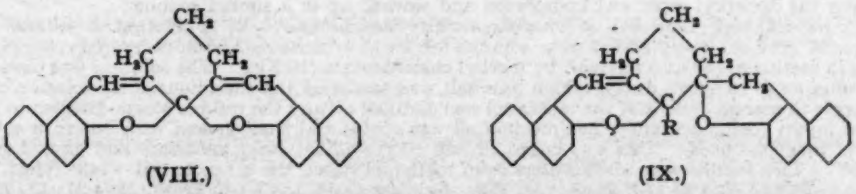
(III*a*.) Colourless in the cold. (III*b*.) Bluish-green on heating.

The action of Grignard solutions on the thermochromic *spiro*pyrans has not hitherto been investigated. We have treated *spiro*di-β-naphthopyran (I) with various Grignard solutions, *e.g.*, phenylmagnesium bromide followed by hydrolysis, and find that the reaction leads to formation of 2 : 3-dihydrofuran derivatives (VI) and not of phenolic compounds (V); (VI, R = Ph) is insoluble in aqueous alkali solution, it is not attacked by ethereal diazomethane solution or by benzoyl chloride in the presence of pyridine and is stable towards methyl sulphate in the presence of alkali. These properties make it improbable that the reaction product has the character of an enol or of a potential enol (V or VII). The diene reaction of (VI) with maleic anhydride was negative.



(IV.) (V.) (VII.) (VI.)

Similarly, the action of Grignard solutions on 3 : 3′-trimethylene*spiro*di-β-naphthopyran (VIII) leads to products which show properties analogous to those of (VI, R = Ph). These compounds are therefore formulated as (IX).



(VIII.) (IX.)

Action of Grignard Reagents on spiro*Di-β-naphthopyran* (I).—(a) *Phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide (magnesium, 0·9 g.; bromobenzene, 9 g.; dry ether,

50 c.c.), the *spiro*pyran (Dickinson and Heilbron, *J.*, 1927, 14; Dilthey and Wizinger, *Ber.*, 1926, **59**, 1856) (2 g.) and dry benzene (20 c.c.) were added. The mixture was refluxed for 2 hours and kept overnight, then decomposed with cold dilute hydrochloric acid and extracted with ether. The ethereal solution was dried and evaporated, and the residue extracted several times with light petroleum (b. p. 30—50°). The petroleum gave, on slow evaporation, colourless crystals which, after repeated crystallisation from petrol (b. p. 100—150°), had m. p. 212—215° (colourless melt). 2-(2′ : 3′-*Dihydro-β-naphthofuran*-2′)-2-*phenyl-β-naphthopyran* (VI, R = Ph) is readily soluble in benzene and xylene but dissolves with difficulty in ligroin. It is insoluble in aqueous sodium hydroxide and dissolves with green fluorescence in concentrated sulphuric acid (Found: C, 87·6; H, 5·2. $C_{31}H_{22}O_2$ requires C, 87·4; H, 5·1%). It is unchanged on further treatment with phenylmagnesium bromide, is not affected by an ethereal solution of diazomethane in the presence or absence of methyl alcohol (cf. Schönberg and Mustafa, *J.*, 1946, 746), and was unchanged when 0·5 g. was refluxed with maleic anhydride (3 g.) in dry xylene for 6 hours or with pyridine (5 c.c.) containing benzoyl chloride (1·5 g.) for 3 hours. Further, 0·5 g., suspended in methyl alcohol (15 c.c.) and treated first with methyl sulphate (3 c.c.), gradually, and then with methyl-alcoholic potassium hydroxide, was recovered unchanged after 2 hours.

(b) p-*Tolylmagnesium bromide.* The p-*tolyl* analogue was obtained in colourless crystals, m. p. 214°, from alcohol–benzene; it was insoluble in aqueous sodium hydroxide and slowly gave a red colour when treated with concentrated sulphuric acid [Found: C, 87·4; H, 5·5; *M* (micro-Rast), 412. $C_{33}H_{24}O_2$ requires C, 87·4; H, 5·4%; *M*, 440].

(c) *α-Naphthylmagnesium bromide.* The *α-naphthyl* compound was obtained in colourless crystals, m. p. 260°, from petrol (b. p. 100—150°); it was insoluble in aqueous sodium hydroxide, gave a red-brown colouration with concentrated sulphuric acid, and was recovered unchanged or almost so when treated with methyl sulphate (Found: C, 87·8; H, 5·1. $C_{35}H_{24}O_2$ requires C, 88·2; H, 5·0%).

Action of Grignard Reagents on 3 : 3′-*Trimethylene*spiro*di-β-naphthopyran* (VIII).—(a) *Phenylmagnesium bromide.* The *spiro*pyran (Dickinson and Heilbron, *J.*, 1927, 1704; Dilthey and Wübken, *Ber.*, 1928, **61**, 965) was treated as mentioned above. The product was decomposed with dilute hydrochloric acid, extracted with ether, dried, and evaporated. The oily residue was extracted with petrol (b. p. 100—150°) and on slow evaporation gave colourless crystals mixed with an oil. The mixture, on further washing with cold ether, formed a solid which crystallised from petrol (b. p. 100—150°) in colourless crystals, m. p. 238°. 2-(2′ : 3′-*Dihydro-β-naphthofuran*-2′)-2-*phenyl*-2′ : 3-*trimethylene-β-naphthopyran* (IX, R = Ph) dissolves in benzene but is difficultly soluble in hot ethyl alcohol and cold ether and insoluble in aqueous sodium hydroxide. It dissolves with an orange colour in concentrated sulphuric acid (Found: C, 87·6; H, 5·8. $C_{34}H_{26}O_2$ requires C, 87·6; H, 5·6%).

(b) *α-Naphthylmagnesium bromide.* The *α-naphthyl* analogue was obtained in colourless crystals, m. p. 305°, from benzene–petrol (b. p. 100—150°); it is insoluble in aqueous sodium hydroxide, dissolves in hot benzene, and with difficulty in petrol, and gives a brownish-red colour in concentrated sulphuric acid (Found: C, 87·9; H, 5·6. $C_{38}H_{26}O_2$ requires C, 88·3; H, 5·4%).—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, CAIRO, EGYPT. [*Received, September 20th*, 1946.]

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1 : 1 : 1-*Trichloro*-2 : 2-*di*-(4-*ω-carbomethoxymethoxyphenyl*)*ethane.* By I. E. BALABAN and F. K. SUTCLIFFE.

STEPHENSON and WATERS (*J.*, 1946, 343) describe a compound prepared by the interaction of 4 : 4′-dihydroxy-DT (as disodium salt) with methyl chloroacetate in methanol solution as 4 : 4′-di-(*ω*-carbomethoxymethoxy)-DT having m. p. 142° (see Errata, 1946). We had previously prepared it by a similar method and found that the dimethyl ester, m. p. 141—143°, was accompanied by a second *substance*, m. p. 82—84°. Stephenson and Waters, however, isolated a single substance, m. p. 142°.

On analysis, both compounds give figures in good agreement for the dimethyl ester, are insoluble in sodium hydrogen carbonate solution, and yield 1 : 1 : 1-*trichloro*-2 : 2-*di*-(4-*ω-carboxymethoxyphenyl*)-*ethane*, m. p. 163—165°, on hydrolysis, identical with the acid prepared from the condensation of phenoxyacetic acid and chloral in the presence of sulphuric acid. The substances, m. p. 82—84° (decomp. 90°), and m. p. 141—143°, are not interconvertible by heating, and the former was recovered unchanged on attempted further esterification on the assumption that it might be the half ester. We are of the opinion, therefore, that they constitute two different forms of the dimethyl ester.

When methyl chloroacetate is brought into reaction with 1 : 1 : 1-trichloro-2 : 2-di-(4-hydroxyphenyl)ethane (as disodium salt) in ethanol solution, *trans*-esterification takes place and the only isolable product is the *diethyl* ester, identical with a specimen prepared from ethyl chloroacetate and the above dihydroxy-compound in ethanol solution. The acid, m. p. 163—165°, esterifies very easily in the presence of a trace of sulphuric acid at ordinary temperature, and consequently, when chloral is condensed with phenoxyacetic acid in the presence of sulphuric acid and the product isolated by the use of methanol, the dimethyl ester and not the free acid is obtained. This was also found to be the case when the dimethyl ester was hydrolysed and worked up in a similar manner.

1 : 1 : 1-*Trichloro*-2 : 2-*di*-(4-*ω-carbomethoxymethoxyphenyl*)*ethane.*—(*a*) A solution of sodium (2·3 g.) in methanol (100 ml.) was added to a solution of 1 : 1 : 1-trichloro-2 : 2-di-(4-hydroxyphenyl)ethane (15·9 g.) in methanol (50 ml.) followed by methyl chloroacetate (16·3 g.). The solution was then heated under reflux for 4—5 hours, during which time salt was deposited and the colour of the solution changed from purple to orange. Most of the methanol was distilled off and the residue steam-distilled to remove excess of methyl chloroacetate. The residual oil was cooled and then shaken with ether; a colourless solid was thus produced. This was collected and recrystallised from methanol and gave 4 g., m. p. 130—136°. Two further recrystallisations from methanol raised the m. p. to 141—143° (yield, 3·1 g.) (Found: C, 51·65; H, 4·24; Cl, 22·68; *M*, 398. Calc. for $C_{20}H_{18}O_6Cl_3$: C, 52·00; H, 4·21; Cl, 23·08%; *M*, 461·5).

The ether solution was washed well with water, dried, and evaporated to give 20 g. of thick, orange-

coloured oil which on treatment with methanol gave 10·1 g., m. p. 72—76°. Three recrystallisations from methanol gave 6 g. of material, m. p. 82—84° (Found: C, 52·62; H, 3·91; Cl, 25·60; 23·97%; *M*, 339). No methoxyl was found by the normal method either with this or with the ester, m. p. 141—143°.

(*b*) The reaction was carried out exactly as in (*a*). After the reflux period, the solution was filtered hot to remove salt and then cooled. The crystalline material was collected, washed with a little methanol, dried, and then extracted with water to remove any sodium chloride. There were obtained 5·9 g., m. p. 127—135°. Two more recrystallisations raised the m. p. to 141—143° (yield, 4·5 g.).

The methanol mother-liquor was removed and the residual paste diluted with ether and the inorganic material collected. The ether solution was washed with N/5-sodium hydroxide (3 × 30 ml.), then water, and dried (Na_2SO_4). Evaporation of the ether gave 10·5 g. of residual oil which was taken up in methanol (20 ml.) and left overnight. The solid was collected and recrystallised from methanol to give 3·5 g. of material, m. p. 76—80°. Two further recrystallisations from methanol raised the m. p. to 82—84° (yield, 3·0 g.).

(*c*) The reaction was carried out as above, but with the methanol replaced by an equal volume of ethanol as solvent. The heating period was cut to 2½—3 hours since the separation of salt and disappearance of purple colour took place more rapidly than with methanol as solvent.

The mixture was filtered hot, and on cooling deposited only a further trace of inorganic material. The solvent was removed under reduced pressure and the residual resin (21 g.) dissolved in ether, washed with N/5-sodium hydroxide (3 × 20 ml.) then water, and dried (Na_2SO_4). After removal of the solvent there remained 13·2 g. of resin which was dissolved in ethanol (25 ml.) and allowed to stand. The solid (5·25 g.) was collected and recrystallised thrice from ethanol to give 2·9 g. of microcrystalline powder, m. p. 82—84°, not depressed on admixture with an authentic specimen of the diethyl ester m. p. 82—84°, as prepared below (Found: C, 53·30; H, 4·68; Cl, 23·12. $C_{22}H_{22}O_6Cl_2$ requires C, 53·9; H, 4·70, Cl, 21·76%).

1 : 1 : 1-*Trichloro*-2 : 2-*di*-(4-*ω*-*carbethoxymethoxyphenyl*)*ethane*.—The reaction was carried out in the same manner as (*c*) above, using sodium (2·3 g.), the dihydroxy-compound (15·9 g.), ethyl chloroacetate (18·4 g.), and ethanol (150 ml.). The amount of the first resin obtained was 20 g., and after washing in ether solution, 12·8 g. This, on treatment with ethanol gave a substance (3·6 g.) which after three recrystallisations from ethanol had m. p. 82—84° (Found: C, 52·97; H, 4·90; Cl, 21·88. Calc. for $C_{22}H_{22}O_6Cl_2$: C, 53·94; H, 4·70; Cl, 21·76%). A mixed m. p. with the substance m. p. 82—84° obtained from (*a*) or (*b*) gave a depression.

1 : 1 : 1-*Trichloro*-2 : 2-*di*-(4-*ω*-*carboxymethoxyphenyl*)*ethane*.—(i) The dimethyl ester, m. p. 141—143° (5 g.), was heated under reflux with a mixture of glacial acetic acid (40 ml.), water (20 ml.), and sulphuric acid (1 ml.; *d* 1·84) for 2 hours. The mixture was then cooled and diluted with water, and the precipitated resin washed well with water. After being dried in a vacuum at 100°, the resin was stirred with benzene; it then crystallised and was recrystallised from benzene–chloroform (1 : 1) and then benzene. There were obtained 3·9 g. (yield, 84%), m. p. 163—165° (Found: C, 50·48; H, 4·03; Cl, 23·8. $C_{18}H_{14}O_6Cl_2$ requires C, 49·83; H, 3·46; Cl, 24·57%). This substance is readily soluble in sodium hydrogen carbonate solution.

(ii) The substance, m. p. 82—84°, from (*a*) above was hydrolysed exactly as in the previous experiment yielding 2·3 g., m. p. 163—165°, which on admixture with the hydrolysis product of the substance of m. p. 141—143° showed no depression.

(iii) Concentrated sulphuric acid (50 ml.) was added to a well stirred water-cooled mixture of phenoxyacetic acid (33 g.), chloral (14·8 g.), and glacial acetic acid (50 ml.) at such a rate that the temperature of the mixture was kept at 30—40°. The resulting solution was kept overnight at room temperature and then poured into water (1 l.) The deposited resin was well washed by decantation and weighed 34 g. Of this, 10 g. were treated with a mixture of benzene (20 ml.) and chloroform (20 ml.), and set aside; 7 g. of crystals, m. p. 158—160°, separated. Two recrystallisations from benzene gave 5·5 g., m. p. 163—165°, identical with the acid from (i) and (ii).

The remaining 24 g. of resin were treated with methanol (70 ml.) and set aside. The solid (14·2 g.) was collected and recrystallised from acetic acid and then ethanol, and gave the dimethyl ester (9·3 g.), m. p. 143—144°; a mixed m. p. with the compound, m. p. 141—143°, from (*a*) or (*b*) gave no depression.

A solution of the acid (m. p. 163—165°; 0·1 g.) in methanol (1 ml.) containing 0·1% of concentrated sulphuric acid was left at room-temperature for 48 hours. The crystalline material was collected and recrystallised from methanol, yielding 0·08 g. (75%) of fine needles, m. p. 141—143°, not depressed on admixture with the dimethyl ester, m. p. 141—143°, prepared from methyl chloroacetate and the dihydroxy-compound in methanol solution.

The acid (1 g.) in ether (20 ml.) together with four equivs. of diazomethane in ether (20 ml.) was left for two days in the ice-box. The ester which had crystallised was collected, and had m. p. 142° (1 g.). When recrystallised from methanol it had m. p. 143—144° (0·8 g.), not depressed on admixture with the dimethyl ester, m. p. 141—143°.

Analyses and molecular weight determinations are by Drs. Weiler and Strauss.—Pharmaceutical Laboratory, The Geigy Company, Ltd., Trafford Park, Manchester, 17. [*Received, August 15th*, 1946.]

The Preparation of Diethyldithiocarbamato-derivatives of 2 : 2′-Dichlorodiethyl Sulphide.

By R. A. Peters and R. W. Wakelin.

The compounds (I) and II) were prepared under physiological conditions of pH and temperature, since they were used in an enzyme research described elsewhere (Peters and Wakelin, Report to Ministry of Supply, by Peters, No. 72). Previously, Holiday, Ogston, Philpot, Stocken, and Peters (1940)

(Report to Ministry of Supply, No. 17) obtained some non-crystalline products which were used in the research for " mustard gas " antidotes.

$NEt_2 \cdot CS \cdot S \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH_2Cl$ (I.)

$NEt_2 \cdot CS \cdot S \cdot CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH_2 \cdot S \cdot CS \cdot NEt_2$ (II.)

2-Chloroethyl 2-(N-Diethyldithiocarbamato)ethyl Sulphide (I).—" Mustard gas " (2 : 2′-dichlorodiethyl sulphide) (2 g.) in ethanol (10 c.c.) was added during 50 minutes with shaking to a solution of sodium diethyldithiocarbamate (6 g., recrystallised from commercial sources) in Ringer phosphate solution (40 c.c.) (pH, 7·3; NaCl, 9 g.; KCl, 0·25 g.; $NaHCO_3$, 0·15 g.; KH_2PO_4, 17·3 g. in 1250 c.c. of water brought to pH 7·35 with 20% NaOH solution) and water (160 c.c.) warmed to 38°. A further small amount of ethyl alcohol (5 c.c.) was used to wash in the remainder of the " mustard gas," and the whole was shaken for 1½ hours at room temperature. The oil was extracted with light petroleum (b. p. 40—60°) and dried (Na_2SO_4). The crude crystals, freed from the light petroleum at the lowest possible temperature, were purified by grinding them with small amounts of absolute ethyl alcohol and filtration upon a sintered glass funnel. Yield of (I), 1·24 g.; 0·5 g. of less pure product (needles) (Found: C, 39·8; H, 6·41; N, 5·1; Cl, 13·1; S, 35·9. $C_9H_{18}NClS_3$ requires C, 39·8; H, 6·63; N, 5·16; Cl, 13·09; S, 35·3%). The *compound* formed platelets from methyl alcohol, m. p. 40·5°.

The compound (I) does not yield chloride ions, and since it does not react with iodine and gives no nitroprusside reaction upon addition of nitroprusside and cyanide, –SH and –S–S groups must be absent, thus confirming the constitution. The rate of formation of hydrochloric acid in 60% ethyl alcohol at 38° for 0·12 ± 0·002M-solutions of " mustard gas " and of (I) (reckoned in terms of Cl content) were substantially the same; k is calculated from the total acid formed (Peters and Walker, *Biochem. J.*, 1923, **17**, 160). For 20—50% hydrolysis, $k = 0·0109$ (for " mustard gas," $k = 0·0104$). This proves that there is still one Cl present from the original " mustard gas."

Longer periods of reaction and shaking gave an impure product melting at 32—33°.

Bis-[2-(N-Diethyldithiocarbamato)ethyl] Sulphide (II).—Crude (I) (1 g.), m. p. 31—35°, was added to a solution of sodium diethyldithiocarbamate (4 g.) in ethyl alcohol (90 c.c.) and water (60 c.c.) and shaken for 2 hours at 38°. The crystals (II) were washed with a small amount of absolute ethyl alcohol and recrystallised from warm ethyl alcohol. The *compound* then had m. p. 65·6° (Found: N, 7·1; Cl, Nil. $C_{14}H_{28}N_2S_5$ requires N, 7·29%). It can also be obtained, as needles, by boiling " mustard gas " (0·5 g.) in ethyl alcohol (40 c.c.) with sodium diethyldithiocarbamate (550 mg.).

Attempts to Prepare the Monohydroxy-compound.—We have tried to make this from the hydrolysate of (I) after warming it with 60% ethyl alcohol as for the determination of k. After extraction with light petroleum and evaporation at low temperature we have obtained oils free from chlorine, which have not yet been crystallised.

We are grateful to Dr. E. Holiday for drawing our attention to the presence of impurities in our light petroleum and for the details of purification following Shepard, Henne, and Midgeley (*J. Amer. Chem. Soc.*, 1931, **53**, 1948). We are also grateful to Experimental Station, Porton, for the C and H analysis of (I), and to Dr. L. A. Stocken for advice and for the S analysis. This work forms part of a programme of research carried out for the Ministry of Supply, to whose Chief Scientific Officer we are grateful for permission to publish.—Department of Biochemistry, Oxford. [*Received, September 5th*, 1946.]

Trityl Derivatives of Xylofuranose: 2-Acetyl 3 : 5-Ditrityl and 2-Methyl 3 : 5-Ditrityl Methylxylofuranoside. By R. J. McIlroy.

It has been reported (McIlroy, *J.*, 1946, 100) that acetylation of tritylated methylxylofuranoside ($\alpha\beta$ mixture) by acetic anhydride in pyridine before isolation of the trityl derivative yielded a non-crystalline product which analysed as diacetyl monotrityl methylxylofuranoside. It has now been found that acetylation of 3 : 5-ditrityl methylxylofuranoside (isolated) gave solely *2-acetyl 3 : 5-ditrityl methylxylofuranoside*, the properties of which are herein recorded. 2-Methyl 3 : 5-ditrityl methylxylofuranoside, previously reported as a syrup (McIlroy, *loc. cit.*), crystallised after being kept for several months and has been further examined.

2-Acetyl 3 : 5-Ditrityl Methylxylofuranoside.—To 3 : 5-ditrityl methylxylofuranoside (1·01 g.) dissolved in dry pyridine (10 c.c.) was added acetic anhydride (15 c.c.). After being kept for 24 hours at room temperature, the solution was poured into well stirred ice-water (500 c.c.). The crystalline precipitate which separated was filtered off, washed thoroughly with water, and dissolved in ether, and the ethereal solution was washed thrice with dilute sodium bicarbonate solution, then with water, and dried (Na_2SO_4). Evaporation of the ether yielded colourless crystals of *2-acetyl 3 : 5-ditrityl methylxylofuranoside* (0·95 g.), which after being recrystallised from ethyl alcohol had m. p. 79—79·5°, $[\alpha]_D^{17°}$ + 2·0° in chloroform (c, 0·98) (Found: trityl, 70·0; acetyl, 18·5. $C_{44}H_{42}O_6$ requires trityl, 70·4; acetyl, 8·6%).

Deacetylation by methyl alcoholic ammonia at 0° gave 3 : 5-ditrityl methylxylofuranoside, m. p. 77—77·5° alone or admixture with an authentic specimen.

2-Methyl 3 : 5-Ditrityl Methylxylofuranoside (McIlroy, *loc. cit.*).—This slowly crystallised after being left in contact with alcohol for some months. After being recrystallised from alcohol it had m. p. 80°, $[\alpha]_D^{16°}$ + 1·6° in chloroform (c, 0·96) (Found: OMe, 9·2; trityl, 73·3. Calc. for $C_{45}H_{42}O_6$: OMe, 9·4; trityl, 73·4%).

It is interesting to note that there is very little difference between the melting points and the specific rotations of 3 : 5-ditrityl, 2-methyl 3 : 5-ditrityl, and 2-acetyl 3 : 5-ditrityl methylxylofuranoside. Moreover there is no marked depression of m. p. when either the 2-methyl or the 2-acetyl derivative is mixed with 3 : 5-ditrityl methylxylofuranoside.—Canterbury University College, Christchurch, N.Z. [*Received, September 5th*, 1946.]

Reduction of αβ-Unsaturated Carbonyl Compounds by Sodium Butoxide. By CH. WEIZMANN, M. SULZBACHER, and E. BERGMANN.

MASTAGLI (*Ann. Chim.*, 1938, **10**, 281; Thesis, Paris, 1938; Mastagli, Charrein, and Lambert, *Compt. rend.*, 1945, **221**, 749) has shown that αβ-unsaturated aldehydes and ketones are reduced to the corresponding saturated alcohols by a boiling benzyl-alcoholic solution of potassium hydroxide; α-alkylcinnamaldehydes give *via* the α-alkylcinnamyl alcohols the 3-phenyl-2-alkylpropanols, and phenyl styryl ketone gives, *via* phenyl 2-phenylethyl ketone, 1 : 3-diphenyl-1-propanol. An equivalent amount of benzyl alcohol is oxidised to benzoic acid.

The same mechanism has been proposed for the Guerbet reaction of butyl alcohol (Weizmann, Bergmann, and Haskelberg, *Chem. and Ind.*, 1937, **56**, 587) for which it was assumed that butaldehyde is formed and " crotonised " to 2-ethyl-2-hexenal which is then reduced to 2-ethylhexanol.

It is desired to record some supporting experiments which were carried out in this laboratory some time ago. Isolated 2-ethyl-2-hexenal is, indeed, reduced to 2-ethylhexanol, and benzylideneacetone to 4-phenyl-2-butanol.

Experimental.—(*a*) 2-Ethyl-2-hexenal (b. p. 65—66°/14 mm; 63·0 g., 0·5 mol.) was added to a solution of sodium (11·5 g., 0·5 mol.) in butanol (74 g.). The mixture was heated at 310° for 7 hours; the pressure reached 50 atm.

Acidic products: Butyric acid, b. p. 63—65°/12 mm. (32 g.); 1-ethylpentane-1-carboxylic acid, b. p. 125—127°/16 mm. (5·0 g.). Neutral products: Butanol (20·7 g., 0·28 mol.); aldehyde C_8 (6·0 g., 0·05 mol.); 2-ethylhexanol (53·0 g., 0·40 mol.).

The aldehyde was not separated from the 2-ethylhexanol, but determined in the mixture by titration with hydroxylamine hydrochloride. A high-boiling fraction (190—240°, 15·0 g.) contained esters and an unsaturated aldehyde, possibly identical with the substance $C_{12}H_{22}O_3$ or $C_{12}H_{20}O$, observed by Weizmann and Garrard (*J.*, 1920, **117**, 329) and Batalin and Slawina (*J. Gen. Chem. Russia*, 1937, **7**, 202).

The amount of 2-ethylhexanol formed (0·40 mol.) corresponds well with that of the acid (total 0·43 mol.). If the aldehyde C_8 is assumed to be the starting material, 9·5% of the latter would have escaped reduction. It is not impossible that the (unsaturated) aldehyde fraction contained some 2-ethylhexanal; but this would be in contradistinction to Mastagli's observations on α-alkylcinnamic aldehydes.

(*b*) A solution of sodium (11·5 g., 0·5 mol.) in butanol (74 g.) was heated with benzylideneacetone (m. p. 42°; 73·0 g., 0·5 mol.) at 300° for 6 hours. The acidic product of the reaction consisted of butyric acid (36·0 g.) and 1-ethylpentane-1-carboxylic acid (2·5 g.), *i.e.*, 0·44 mol. (calculated as butyric acid).

From the neutral product were isolated by means of a Widmer column: Butanol (33·0 g., 0·45 mol.); 2-ethylhexanol (5·2 g., 0·04 mol.); 4-phenyl-2-butanol (22·5 g., 0·15 mol.); benzylideneacetone (5·0 g., 0·034 mol.).

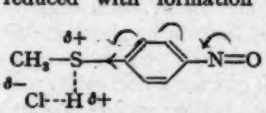
The resinous residue boiled above 200° under 16 mm. pressure.

The 4-phenyl-2-butanol boiled at 115—117°/13 mm. and was identified through its phenylurethane, m. p. 116—117°.

Corresponding to the 0·04 mol. of 2-ethylhexanol formed from butyl alcohol, only 0·04 mol. of butyric acid should have been obtained (Guerbet reaction). Approximately 0·40 mol. of butyric acid was formed, therefore, in the reduction of the unsaturated ketones. The yield of 4-phenyl-2-butanol should also have been 0·40 mol. (Found: 0·15 mol.); the resin formation accounts for the balance.—GROSVENOR LABORATORY, LONDON, S.W.1. [*Received, September 30th*, 1946.]

The Preparation and Some Reactions of 4-Nitrosothioanisole. By HERBERT H. HODGSON, DOUGLAS D. R. SIBBALD, and ERNEST W. SMITH.

THE 3-halogeno-4-nitrosoanisoles had previously been found to lose their methyl groups on keeping, or on heating under reflux with dilute mineral acids, and to be converted into the 3-halogenobenzoquinone 4-oximes (Hodgson and Kershaw, *J.*, 1930, 1969). Similarly, a solution of 3-fluoro-4-nitrosoanisole in methyl alcohol was found to be rapidly converted into 3-fluoro-4-nitrosophenol when shaken with concentrated hydrochloric acid (Hodgson and Nicholson, *J.*, 1940, 1268). It was hoped, therefore, that similar treatment of *4-nitrosothioanisole* would afford either 4-nitrosophenylthiol or benzothioquinone 4-oxime; instead, however, the methylthio-group resisted disruption, while the nitroso-group was reduced with formation of *4 : 4'-dimethylthioazoxybenzene*. The latter was also synthesised by condensation of *4-hydroxyaminothioanisole* with 4-nitrosothioanisole. This reduction of the nitroso-group by only methyl alcohol in the presence of hydrogen chloride is noteworthy, and must be ascribed to recession of electrons from the nitroso-group caused by the methylthio-group, which in turn must be due to incipient salt formation at it, whereby the anionoid character of the methylthio-group is transformed into the kationoid character of the incipient sulphonium group (see inset) (cf. Hodgson and R. Smith, *J.*, 1937, 1634, for salt formation at the phenylthio-group).



Experimental.—Preparation of 4-hydroxyaminothioanisole. 4-Nitrothioanisole (4 g.), dissolved in ethyl alcohol (15 c.c.), was stirred with a solution of ammonium chloride (0·5 g.) in water (12 c.c.), and the mixture heated until the finely divided suspension of the thioanisole had melted; zinc dust (*ca.* 5 g.) was then added in small portions with vigorous agitation until the supernatant liquor was almost colourless. After hot filtration and washing of the residue with hot ethyl alcohol (15 c.c.), the combined filtrate and washings were chilled by external ice, the light orange separation of crude solid *4-hydroxyaminothioanisole* filtered off, and washed with a little cold benzene until colourless, minute amounts of azo- and azoxy-compounds being thereby removed; it crystallised from aqueous 50% ethyl alcohol in colourless, iridescent plates, m. p. 85° (to a red liquid with subsequent decomposition) (Found: N, 9·2; S, 20·8. C_7H_9ONS requires N, 9·0; S, 20·6%), which gave a crimson-magenta colour with

concentrated sulphuric acid, changing to a blue-violet on heating, and to light yellow on dilution with water.

4-*Nitrosothioanisole* was obtained when a solution of 4-hydroxyaminothioanisole (0·8 g.) in ethyl alcohol (10 c.c.) was added gradually at 0° to a well-stirred solution of anhydrous ferric chloride (3 g.) in water (7 c.c.) containing floating ice; it separated in green crystals which melted below room temperature (Found: N, 9·3; S, 21·1. C_7H_7ONS requires N, 9·15; S, 20·9%) and were volatile in steam. 4 : 4′-*Dimethylthioazoxybenzene* resulted when solutions of equivalent quantities of 4-hydroxyaminothioanisole and 4-nitrosothioanisole in methyl alcohol were mixed together; it crystallised from methyl alcohol in pale yellow micro-needles, m. p. 133° (Found: N, 9·9; S, 22·3. $C_{14}H_{14}ON_2S_2$ requires N, 9·65; S, 22·1%), which gave a magenta-violet colour with concentrated sulphuric acid changing to violet on heating, and, on dilution with water, first to blue and then to yellow.

Action of hydrogen chloride on 4-nitrosothioanisole. Dry hydrogen chloride was passed into a solution of 4-nitrosothioanisole in methyl alcohol for 1 hour; the solution became red and deposited iridescent colourless plates of 4 : 4′-dimethylthioazoxybenzene, m. p. and mixed m. p. with authentic specimen above, 133° (Found: N, 9·8; S, 22·2%).

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.—
TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, October 2nd*, 1946.]

Macromolecules synthesised by Micro-organisms.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON DECEMBER 6TH, 1946, AND IN CAMBRIDGE ON JANUARY 17TH, 1947.

By M. STACEY, PH.D., D.Sc., F.R.I.C.

IN the past, the main effort dealing with the synthetic activities of bacteria has been directed towards solving the complex problems of their intermediate metabolism and in controlling fermentation reactions. In recent years a good deal of knowledge has been obtained regarding the growth requirements of bacteria particularly in respect to their essential amino-acids and " vitamins ". The synthetic activities of moulds (or the lower fungi), on the other hand, have been studied in a systematic way by H. Raistrick and his associates whose work has revealed the structures of many interesting crystalline metabolic compounds including pigments, quinones, bacteriostatic agents, carbohydrates, etc. This lecture deals with the chemical approach towards solving some of the problems of the architecture of the macromolecules of which the diverse components of the microbial cells are constituted.

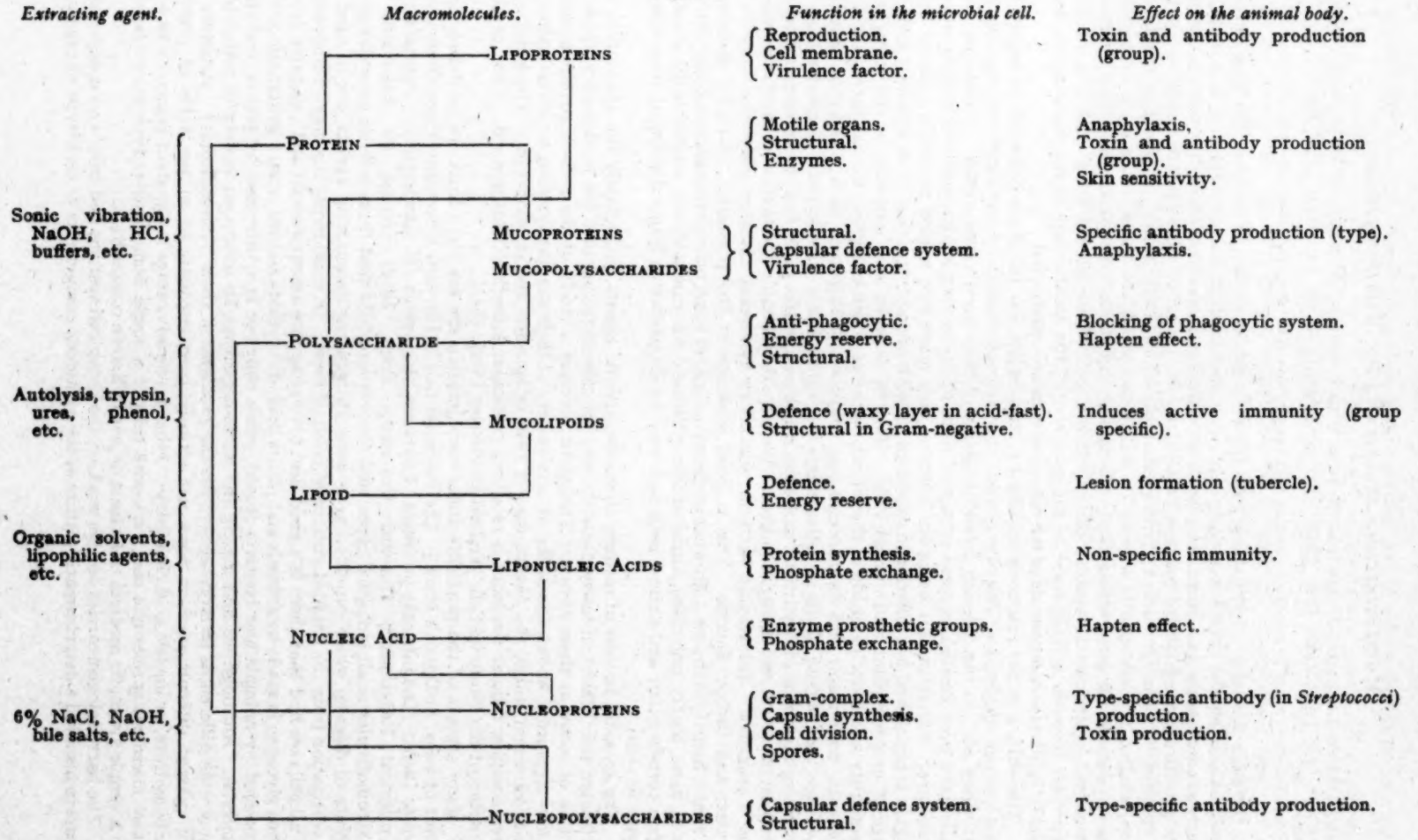
The nature of the reactions studied by biochemists has led them generally to regard the bacterial cell simply as a " bag of enzymes " carrying out respiratory, synthetic, and reproductive activities, etc., in the complex colloidal system of their metabolism media. Frequently these cells have been treated as some primitive form of life having a comparatively simple cellular structure. Far from this being so, however, one must now regard microbial cells as being highly complex and not differing in essentials in cell structure, function, or morphology from the highest evolved plant and animal cells. Most of us have seen evidence of the remarkable versatility and tenacity of life of the moulds, some of which can grow, for example, in organic solvents, on phenol, and on concentrated solutions of sulphuric acid. There is abundant evidence that almost all these cell systems can synthesise a wide variety of giant molecules, including their own autosynthetic molecules which behave like genes and chromosomes, from the simplest of carbon and nitrogen sources. We have the example of one class of micro-organisms, the " primitive " autotrophic bacteria, which can synthesise complex molecules from rocks, water, and carbon dioxide. This is good evidence of the possession of highly developed systems, and there is now a growing tendency to regard some micro-organisms as being derived from more highly organised forms of life. Viruses, for example, are undoubtedly parasitic upon certain plant and animal cells and may be degenerative forms descended from similar types of cells.

The splendid success of modern chemotherapeutic agents, particularly the antibiotics, has attracted the interest of many chemists who are now inquiring into the fundamental mode of action of many of these agents. This work involves a study of the growth requirements of micro-organisms, knowledge of the diverse variety of their enzyme systems, an investigation of their variation and of the mechanisms of their adaptation and reproduction. The kinetics of their complex cellular reactions is receiving particular attention (Hinshelwood, " The Chemical Kinetics of the Bacterial Cell," Oxford University Press, 1946).

Many aspects of the problems under consideration are set forth from the bacteriologist's point of view, in Dubos's book (" The Bacterial Cell ", Harvard University Press, Monograph No. 6, 1945). The intricate problems of immune phenomena (K. Landsteiner, " Specificity of Serological Reactions ", Harvard University Press, 1946) involve the behaviour of macromolecules of all biological types, and there is no doubt that these cellular constituents of agents of disease, which provide our present antigens or immunising agents, are in need of investigation from the detailed structural point of view. In considering the major components of all cells we find that there is a good deal of overlapping among animal and vegetable types. Thus glycogen is made by animals and plants (including yeasts and bacteria); hyaluronic acid is produced by animals and bacteria (cocci), while cellulose is synthesised by plants (including bacteria). Although we find among the micro-organisms an enormous variety of cells which show wide differences in morphology, yet the problems of their " bio-molecular " structure do not present difficulties which have not already been encountered in the fields of protein, carbohydrate, or nucleic acid chemistry. Indeed, one advantage is apparent inasmuch as with many microbial species one can work with cells of a single homogeneous type grown *in vitro* on a simple synthetic medium or at least on one of known composition.

The bacteriologist carries out his work on the living cell systems and from a vast experience bears in his mind a diagrammatic picture of the numerous components of each type of organism

Figure 1.


Extracting agent.
Macromolecules.
Function in the microbial cell.
Effect on the animal body.
Lipoproteins
Reproduction.
Cell membrane.
Virulence factor.
Toxin and antibody production (group).
Protein
Motile organs.
Structural.
Enzymes.
Anaphylaxis.
Toxin and antibody production (group).
Skin sensitivity.
Sonic vibration, NaOH, HCl, buffers, etc.
Mucoproteins
Mucopolysaccharides
Structural.
Capsular defence system.
Virulence factor.
Specific antibody production (type).
Anaphylaxis.
Polysaccharide
Anti-phagocytic.
Energy reserve.
Structural.
Blocking of phagocytic system.
Hapten effect.
Autolysis, trypsin, urea, phenol, etc.
Mucolipoids
Defence (waxy layer in acid-fast).
Structural in Gram-negative.
Induces active immunity (group specific).
Lipoid
Defence.
Energy reserve.
Lesion formation (tubercle).
Organic solvents, lipophilic agents, etc.
Liponucleic Acids
Protein synthesis.
Phosphate exchange.
Non-specific immunity.
Nucleic Acid
Enzyme prosthetic groups.
Phosphate exchange.
Hapten effect.
6% NaCl, NaOH, bile salts, etc.
Nucleoproteins
Gram-complex.
Capsule synthesis.
Cell division.
Spores.
Type-specific antibody (in Streptococci) production.
Toxin production.
Nucleopolysaccharides
Capsular defence system.
Structural.
Type-specific antibody production.

as exemplified particularly by the coccus (see Gay, "Agents of Disease and Host Resistance", Thomas, 1935, p. 527). The bacteriologist's representation has been gained by cytological and staining methods, and recent electron-micrographs (Professor W. T. Astbury, private communication) show that, in the coccus at any rate, the locations of some of the components such as the capsular substances are substantially correct.

In the present account of these macromolecules it will be convenient to consider separately the various components of the cell and to confine attention to those constituents on which we have some precise structural information. At present only in the carbohydrate group have any extensive studies been made.

From the chemist's point of view we can consider the nature of the main parts of the cell as deduced by qualitative and serological methods.

These different parts of the cell are by no means sharply differentiated, and in any colony or metabolism solution of such rapidly self-reproducing systems, where the cells must be of different ages, it will be apparent that cell composition is unlikely to be uniform. Nevertheless there is good evidence of a cell wall, so that we can usually distinguish between extra- and intra-cellular substances. In some organisms motile organs, or flagella, appear to exist, while in others there are well-defined regions outside the cell wall consisting of the capsular substance. Inside the cell membrane is the somatic part or protoplast in which nuclear structures are less clearly defined, though sound cytological evidence regarding the bacterial nucleus is now appearing (Robinov, Addendum in Dubos, *op. cit*; Dr. H. Henry, private communication).

There is no doubt that the macromolecular constituents are frequently in firm combination with one another and that the nature of any complex, such as a mucoprotein or a lipoprotein, is largely determined by the method of its extraction and isolation for which we need to choose a technique which has been found appropriate by past experience for some particular type of cell. Numerous processes for disintegrating cells and liberating their constituent macromolecules into solution are now available. We have, for example: freezing and thawing; autolysis; extraction with water, acids, alkalis, and buffers; sonic vibration; proteolytic hydrolysis; extraction with detergents, ethylene glycol, phenol, urea, guanidine, etc. When part or all of the components of the cells are solubilised, the usual methods for isolating proteins, nucleic acids, and polysaccharides can then be followed.

The nature of any complex molecule profoundly alters its biological function; this fact is of great importance in immunology, particularly from the point of view of vaccine and toxin production. In the past the main emphasis has been placed on the purification of the proteins, polysaccharides, etc., as essential entities, but the present trend is towards the production of complexes containing mainly one constituent combined with "prosthetic groups". Such complexes may fulfil special biological functions. The numerous macromolecular types which can be isolated from micro-organisms are shown in Figure 1, in which are indicated also in a general way some of their functions and effects.

In the past, chemical researches on many micro-organisms have been difficult owing to lack of sufficient amounts of bacterial cells and the studies have thus, of necessity, been conducted largely by micro-methods. Mass production of cells such as *Mycobacterium tuberculosis* is now an established process so that chemical studies can go ahead much more rapidly. Many of the macromolecules are obtained in colloidal solution in water or in salt solutions, and we meet all the problems encountered in protein chemistry complicated by the added difficulties inherent in polysaccharide or nucleic acid chemistry. Future progress in the field will follow closely the advances in general protein, polysaccharide, and nucleic acid chemistry on both the physical and the structural side.

Extracellular Products.

Great care is needed in deciding whether any product is truly extracellular, for large molecules may originate (*a*) by formation in the cell and then by proceeding by dialysis from within, outwards through the cell membrane; (*b*) by being synthesised in the metabolism solution by the agency of extracellular enzymes; and (*c*) by being broken away from the actual cellular structural components by the action of the autolytic cell enzymes such as the carbohydrases, nucleases, proteinases, etc.

One of the most widely known extracellular products is commercial "tuberculin" which is used for diagnosing tuberculosis infection especially in dairy cattle. The cell-free filtrates of numerous strains of *M. tuberculosis* have been intensively investigated by F. Seibert, who showed that tuberculin was composed essentially of proteins which were present in close association with nucleic acids and polysaccharides. It was shown by Seibert (*Chem. Reviews*,

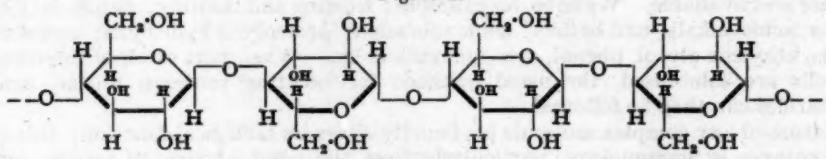
1944, **38**, 107) that the proteins such as the "Purified Protein Derivative" (or "P.P.D.") were highly serologically active and able to elicit skin sensitivity reactions in certain patients upon subcutaneous injection. By electrophoretic technique, Seibert and Munday (*Amer. Rev. Tuberc.*, 1932, **25**, 724; Seibert, Pederson, and Tiselius, *J. Exp. Med.*, 1938, **68**, 413) were able to separate from P.P.D. a crystalline protein and to show that this was the true tuberculin and that the deoxyribonucleic acid and polysaccharide components were serologically inactive.

Diphtheria toxin is an extracellular product of great importance since on injection into animals it gives diphtheria antitoxin used in the prophylaxis of diphtheria. It is the only bacterial extracellular toxin on which we have adequate criteria of purity and composition. The investigations described by Eaton (*Bact. Rev.*, 1938, **2**, 3) and Pappenheimer (*J. Bact.*, 1942, **63**, 373) show that diphtheria toxin is a well-defined protein molecule. During the war other remarkable bacterial toxins have been investigated and doubtless will be reported on in due course.

Bacterial Cellulose.

This polysaccharide is probably one of the best examples of a true extracellular bacterial product. It is obtained in *ca.* 5% yield in the form of a tough membrane when *Acetobacter.* and other species are grown aerobically on hexoses, particularly fructose, and on the sugar alcohols. Hibbert and Barsha (*Canadian J. Res.*, 1934, **10**, 170) conducted a thorough investigation of bacterial cellulose produced in the form of a vast number of closely compacted membranes which appeared to give to the product a somewhat higher chemical stability than that of plant cellulose. Applications of the methods well known in cellulose chemistry, such as acetylation, acetolysis, methylation, hydrolysis, oxidation, *X*-rays, electron microscope, etc., have revealed that bacterial cellulose was chemically identical with cotton cellulose (Figure 2).

Figure 2.



Cellulose.

Interesting results were obtained by Franz and Schiebold (*J. Macromol. Chem.*, 1943, **1**, 4) in their *X*-ray and electron-microscope studies on bacterial cellulose. It was shown with some specimens that bacterial cells were connected by single fibres about 200 A. wide which became woven together. Recently, bacterial cellulose has been synthesised by resting cells of *B. xylinum* (Hestrin, Aschner, and Mager, *Nature*, 1947, **159**, 64).

Mould Polysaccharides.

Mould polysaccharides appear to be true extracellular products, and those so far studied present interesting types of complex carbohydrate structure. When produced in a liquid medium, mould polysaccharides usually have relatively small molecular weights due, possibly, to the comparatively long period required for metabolism during which the lytic enzymes degrade the initial macromolecules. Most moulds produce a complex mixture of polysaccharides, the proportion of any one component depending upon the period required for growth. The biological function of the extracellular mould polysaccharide is unknown, it being generally assumed to act as a reserve carbohydrate. On solid medium it appears to behave as a mucilaginous "defensive colloid".

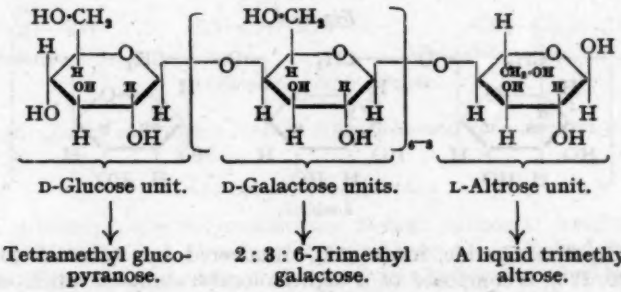
One can apply to the mould polysaccharides the well-tried methods known in polysaccharide chemistry. These methods involve fractionation with solvents, ultracentrifugation, electrophoresis, diffusion, etc., followed by hydrolysis and identification of the monosaccharide components by formation of characteristic crystalline derivatives or by paper chromatography. Acetylation, acetolysis, and methylation studies give an assay of the repeating units and of the side-chain and terminal residues. In neutral polysaccharides these also can often be measured by oxidation methods, particularly the periodic oxidation method of Brown, Dunstan, Halsall, Hirst, and Jones (*Nature*, 1945, **156**, 785).

Some examples of the types of structures of the repeating units in mould polysaccharides are shown in Figures 3—6.

Varianose.

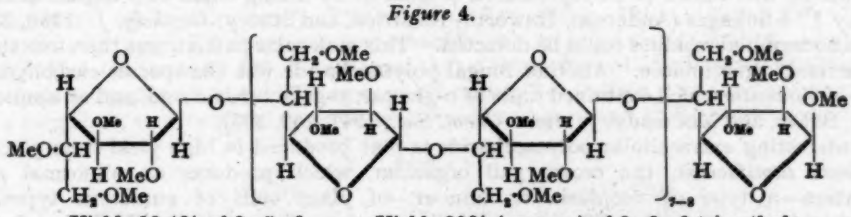
Varianose, produced from D-glucose by *Penicillium varians* G. Smith, consists of a chain of 6—8 β-D-galactopyranose units (Haworth, Raistrick, and Stacey, *Biochem. J.*, 1935, **29**, 2668)

Figure 3.



joined by 1 : 4 linkages with a D-glucopyranose residue at the non-reducing end and an L-altrose unit (Stacey, unpublished results) at the reducing end.

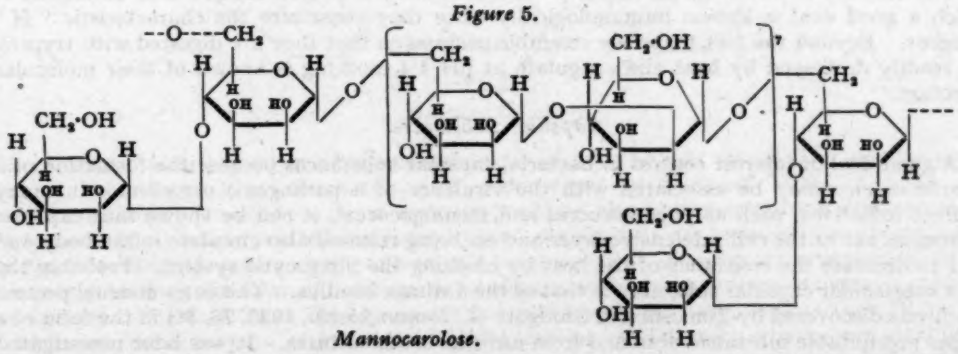
Figure 4.



Methylated galactocarolose.

Galactocarolose was produced from D-glucose by *P. Charlesii* G. Smith (Haworth, Raistrick, and Stacey, *Biochem. J.*, 1937, **31**, 640), and from a study of the methylated polysaccharide the minimum repeating unit was shown as a chain of 9—10 galactofuranose units linked through the 1 and 5 positions. This appears to be one of the rare cases where D-galactose is found to occur naturally in the furanose form (Figure 4).

Figure 5.

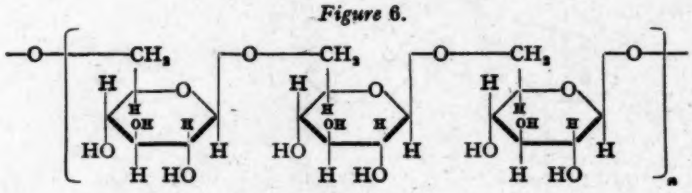


Mannocarolose.

Mannocarolose is a mannan produced along with galactocarolose from D-glucose by *P. Charlesii* G. Smith, and was reported (Haworth, Raistrick, and Stacey, *Biochem. J.*, 1935, **29**, 612) to consist of a straight chain of D-mannopyranose units linked through the 1 : 6-positions. The trimethyl mannose constituent of the methylated mannocarolose was noted by Haworth, Hirst, Isherwood, and Jones (*J.*, 1939, 1878) to differ from an authentic specimen of 2 : 3 : 4-trimethyl mannose. A recent re-investigation of the hydrolysed methylated

mannocarolose (Stacey, unpublished results) has revealed that the trimethyl mannose fraction consisted of equimolecular amounts of the 2 : 3 : 4- and the 3 : 4 : 6-trimethyl derivatives and also it was shown that the origin of the 2 : 3-dimethyl mannose component was not due to incomplete methylation. Accordingly, the branched chain structure (Figure 5) is now thought to represent more closely the repeating unit in this mould mannan.

Figure 6.



Luteose.

The unique acid-polysaccharide, luteic acid, discovered by Raistrick and Rintoul (*Phil. Trans.*, 1931, *B*, **220**, 225), is composed of a high molecular complex which was shown to be a polyglucose (" luteose "), esterified with malonic acid in the proportion of 2 molecules of glucose per molecule of malonic acid. Mild acid or alkaline hydrolysis readily destroyed the remarkable viscosity of aqueous solutions of luteic acid and split off the malonic acid residues. The structure of the luteose was shown to be represented (Figure 6) by a long chain of β-D-glucose residues joined by 1 : 6-linkages (Anderson, Haworth, Raistrick, and Stacey, *Biochem. J.*, 1939, **33**, 272) in which no terminal residues could be detected. This molecular pattern was therefore that of a " polymerised " gentiobiose. Another fungal polysaccharide was the specific carbohydrate of *Coccidioides immitis* which contained units of D-glucose, D-galacturonic acid, and an amino-sugar (Hassid, Baker, and McCready, *J. Amer. Chem. Soc.*, 1941, **149**, 303).

An interesting extracellular polysaccharide is that produced in high yield from glucose by *Phytomonas tumifaciens*, the crown gall organism, which produces an abnormal growth proliferation—a type of neoplasia or tumour—of plant cells of numerous types. The polysaccharide was shown by diffusion and sedimentation-velocity studies (McIntire, Peterson, and Riker, *J. Biol. Chem.*, 1942, **143**, 491) to consist of a chain of 22 glucose units.

Its optical behaviour in water and cuprammonium solution so closely resembled that of 2-methyl β-methylglucoside (Reeves, *J. Biol. Chem.*, 1944, **154**, 49) that it appeared that the D-glucopyranose residues were linked chiefly through the 1 : 2-positions.

Extracellular polysaccharides probably play an imporant rôle in soil and may assist in conservation of moisture.

Flagella.

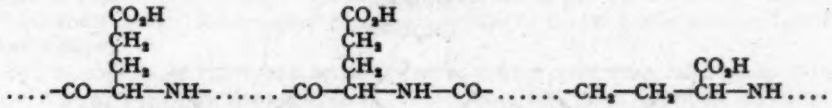
The motility of bacteria, particularly the *Salmonella*, is due to the presence of flagella of which a good deal is known immunologically since they constitute the characteristic " H " antigens. Beyond the fact that they resemble proteins in that they are digested with trypsin, are readily destroyed by heat and coagulate at pH 4·4, nothing is known of their molecular structure.

Capsular Substances.

A good deal of interest centres in bacterial capsular substances because the formation of a capsule *in vivo* may be associated with the virulence of a pathogenic organism. In many virulent infections, such as pneumococcal and meningococcal, it can be shown that capsular substances act as the cell's defensive layer and on being released also circulate in the body and tend to decrease the resistance of the host by blocking the phagocytic system. Probably the most spectacular capsular substance is that of the anthrax bacillus. This is an unusual protein which was discovered by Tomcsik and Szongott (*Z. Immunforsch.*, 1933, **78**, 80) in the form of a copper precipitable substance obtained from anthrax broth cultures. It was later investigated by Ivanovics and his colleagues (*ibid.*, 1937, **90**, 304; 1940, **97**, 402, 442; **98**, 373), and was shown to be a polyglutamic acid composed solely of unusual *d*(+)-glutamic acid residues. None of the usual proteolytic enzymes will attack it. Hanby and Rydon (*Biochem. J.*, 1946, **40**, 297) described methods for the isolation and purification of the undegraded *B. anthracis* capsular protein. They showed that different strains of *B. anthracis* give an identical product which they confirmed was composed solely of *d*(+)-glutamic acid residues. It had a molecular weight of 50,000 and was a long chain molecule made up of α-peptide chains of 50—100 *d*(+)-glutamic acid

residues which were joined together by γ-peptide chains of *d*(+)-glutamic acid residues (Figure 7).

Figure 7.



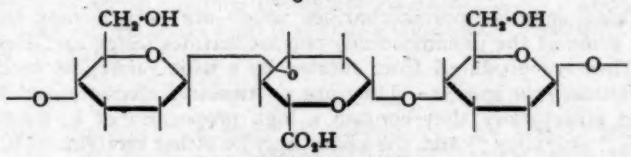
Anthrax Capsular Protein.

Other ærobic sporulating organisms such as *B. subtilis* and *B. mesentericus* produce a similar polyglutamic acid.

Capsular Polysaccharides.

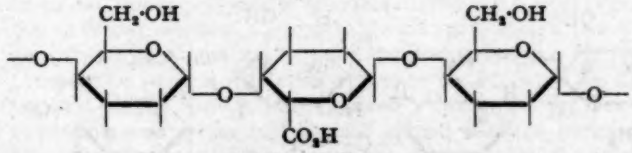
Most capsular substances are polysaccharides of high molecular weight, and problems of bacterial encapsulation in general, have been the most thoroughly studied in the pneumococcus group. The immunological significance of these polysaccharides was discovered by Avery and Heidelberger (*J. Exp. Med.*, 1923, **38**, 81) who showed that each pneumococcus type owed its sharp serological specificity to the special structural characteristics of the complex carbohydrate. More than forty types of pneumococcus have now been recognised, and the remarkable differences and similarities between the capsular polysaccharides are shown in Boyd's "Fundamentals of Immunology" (Interscience, New York, 1943). From the structural aspect, only the Type III specific polysaccharide has as yet been examined. Reeves and Goebel (*J. Biol. Chem.*, 1941, **139**, 511) showed that it is constituted of cellobiuronic acid residues linked through position 3 of the glucuronic acid moiety to position 1 in the next glucose unit giving a long chain structure which contains alternate 1 : 3-β-D- and 1 : 4-β-D-linkages (Figure 8).

Figure 8.



Type III Polysaccharide.

Figure 9.



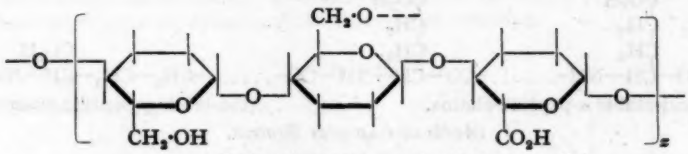
Oxidised Cellulose.

Hexuronic acids are found in other pneumococcus capsular polysaccharides, *e.g.* D-galacturonic acid in the Type I polysaccharide and D-glucuronic in those of Types II, VIII, etc., while Friedlander's bacillus—a Gram-negative bacillus—also synthesises uronic acid-containing polysaccharides closely related serologically and structurally to some of the pneumococcal polysaccharides. Another characteristic of pneumococcus capsular polysaccarides is the frequent occurrence in them of hexosamine constituents, the amino-groups of most of which are acetylated. Others, such as Type I, contain *O*-acetyl groups and some, such as Type IV, possess a high phosphorus content. Close structural and serological relationships have been established between oxidised cellulose (Figure 9), the polysaccharide of *Rhizobium radicicolum* (Figure 10), and the Pneumococcus Type III polysaccharide (Figure 8) (Schlüchterer and Stacey, *J.*, 1945, 776).

Dr. B. R. Record (private communication) has recently compared, in the ultracentrifuge and by diffusion measurements, some physical properties of relatively undegraded samples of the pneumococcus polysaccharides Types I, II, and III, prepared by the lecturer. Despite the big differences in chemical structure the physical constants and molecular shapes were very similar.

The great dependence of sedimentation velocity on concentration, typical of long chain molecules, was a characteristic of all three polysaccharides. A similar effect was found in the diffusion

Figure 10.



Rhizobium *Polysaccharide.*

constants though in the other direction, *i.e.*, of increasing rate of diffusion with increase in concentration, and it was important to extrapolate these two constants (sedimentation and diffusion) to zero concentration in the case of such abnormal behaviour in order to calculate molecular weights such as those shown in Figure 11.

Figure 11.

Pneumococcus Polysaccharides. Sedimentation and Diffusion Data. (Dr. B. R. Record.)

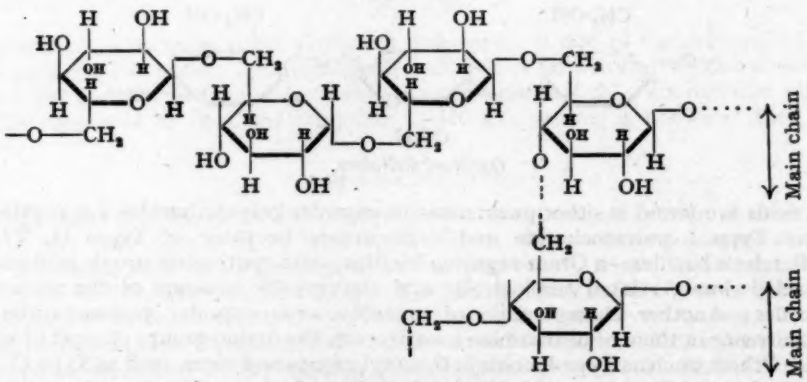
Type.	$S_{20} \times 10^{13}$ ($c \to 0$).	$D_{20} \times 10^{7}$ ($c \to 0$).	Molecular Weight.	Frictional Ratio.
I.	6·5	2·00	170,000	3·2
II.	7·2	0·75	500,000	6·0
III.	4·3	1·60	140,000	4·3

The large frictional ratios indicated a wide departure from linearity in the shape of the molecules which were probably very elongated.

Bacterial Dextrans.

These are striking capsular polysaccharides which are polyglucoses showing serological relationships with some of the pneumococcus polysaccharides (Sugg and Hehre, *J. Immunol.*, 1942, **43**, 119). They are produced from sucrose by a wide variety of species including the *Leuconostoc* and *Betabacteria* species. They are particularly characterised by having a high dextrorotation and structurally they contain a high proportion of 1 : 6 α-D-glucose linkages (*i.e.*, isogentiobiose " polymers ") and the chain may be either straight or branched. A type of the latter is shown for a *L. mesenteroides* dextran (cf. Evans and Hibbert, " Advances in Carbo-

Figure 12.



L. mesenteroides *Dextran.*

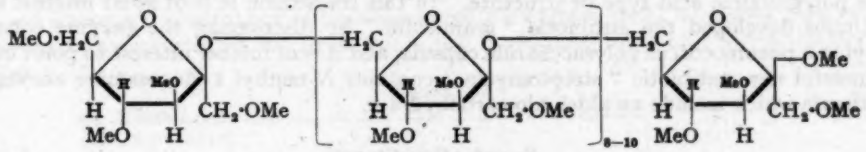
hydrate Chemistry ", Vol. II, p. 203) in Figure 12. Lively interest is attached to dextrans because they can be degraded to give a product which appears to be an excellent substitute for plasma in blood transfusion. Dextrans can be synthetised enzymically and it would appear that direct phosphorylation processes are not involved. Recently we have made the striking observation that the so-called " dextran synthesis factor " is *p*-aminobenzoic acid, a fact which is of interest concerning the mode of action of the sulphonamides.

Levans.

Bacterial levans form the mucilaginous capsules of numerous bacteria. The occurrence of fructosans in plants (Macdonald, " Advances in Carbohydrate Chemistry ", Vol. II., 1946) is widespread and it is well known that numerous groups of bacteria also can produce fructosans of the levan type.

Levans, as well as dextrans, can be produced only from sucrose or raffinose as substrate and they vary considerably in their physical properties. The most common levan-synthesising organisms belong to the non-pathogenic ærobic " potato " group, *e.g.*, *B. mesentericus* and *B. vulgatus*, in addition to *B. subtilis*, the hay bacillus. Early work on the structure of levans is due to Tipson and Hibbert, to Haworth, Hirst, and Challinor, and also to Peat, Stacey, and Lyne (Evans and Hibbert, *loc. cit.*). These workers discovered a previously unknown structure, similar to inulin in that it provides an example of the natural occurrence of fructose in the furanose form. In levans the fructo-furanoses are linked in the 2 : 6-positions in a chain of 10—12 contiguous units.

Figure 13.



Methylated Levan.

Notable also among the levan producers are the plant pathogens, *Ps. pruni*, *Ps. prunicola*, and *Ps. mors prunorum*, and in these the repeating units are identical. Physical differences appear to be due to the differences in the degree of aggregation of the repeating units, a view supported by the electron micrographs (Ingleman and Siegbahn, *Nature*, **1944**, **154**, 237). Among the encapsulated pathogens which produce levans are *Streptococcus bovis* and *Str. viridans*. The levan type of complex molecule has been produced enzymically (Hestrin, Avineri-Shapiro, and Aschner, *Biochem. J.*, **1943**, **37**, 450).

Hyaluronic Acid.

Certain so-called " mucoid " strains of *Streptococcus* (A and C strains) produce the polysaccharide-acid, named by Meyer and Palmer (*Amer. J. Ophthal.*, **1936**, **19**, 859), " hyaluronic acid ". The substance is a normal component of the animal body in which it forms the ground substance of connective tissues and skin, and it is the main building constituent of the umbilical cord. It is claimed to be a linear polymer of glucuronic acid and *N*-acetyl glucosamine residues. It shows in aqueous colloidal solution a remarkable viscosity which can be broken either by simply shaking the solution in air, or much more dramatically by a spreading-factor enzyme " hyaluronidase " present in venoms, bacterial exudates, testes, etc. We find that it is a most labile carbohydrate and so far cannot be examined structurally by the usual methylation technique. The repeating unit seems to be small and to contain, perhaps, a stable " core " which is protected by other residues. Being a normal constituent of the animal body it does not stimulate antibody production, and streptococci possessing such a protective capsule are probably more pathogenic on that account. It presents many interesting problems for the physical chemist. For example, it forms apparent fibres which under the *X*-rays are not true oriented fibres (Professor W. T. Astbury, private communication). As in many natural complex acid polysaccharides the carboxyl groups are free and engage in salt linkage and hydrogen-bond formation.

Acid-fast " Capsular " Substances.

A further possible capsular substance is the so-called " waxy " layer of the acid-fast organisms. It is very doubtful whether this is a true capsule (Dubos, " The Bacterial Cell ", Harvard University Press, 1945) and it is almost certainly not true that all the fatty acids are located at the surface layer. On the other hand we ourselves have obtained evidence that the acid-fast fatty acids, *e.g.*, mycolic acid, are located mainly at the surface and that these are in close association with deoxyribonucleic acid and a polysaccharide (Haworth, this vol., p. 582). The lipoids can stimulate giant-cell formation, while the free fatty acids, natural and synthetic, which are of branched chain type, can produce tubercular lesions (Robinson, *Nature*, **1946**, **158** 815). The polysaccharide is of a most unusual type and it is probably esterified with mycalic

acid to form a giant molecule of high chemical stability. The mycolic acid when freed from the carbohydrate appears to have some acid-fast properties. Related substances are found in *Mycobacterium phlei* and in the leprosy bacillus (*M. lepræ*).

At this stage we can make some generalisations regarding the nature of capsular substances. They are chiefly highly viscous complex " hapten " carbohydrates having a main structural architecture resembling that of the plant gums. The macromolecular state and the capacity to stimulate antibody production appear to depend on the presence in the molecule of a bound prosthetic group. Frequently they contain hexuronic acids (in which the carboxyl groups are free to engage in salt formation and hydrogen bonding) and amino-sugars in which the amino-group is usually substituted by an acetyl residue. A high degree of branching occurs in most types. The monosaccharide units may possess both pyranose and furanose forms and almost every kind of positional linkage, though invariably there is found a high proportion of glycosidic linkages.

It is clear that micro-organisms have evolved a mechanism for the synthesis of capsular structures which are not generally susceptible to enzymic cleavage. This is particularly true for the polyglutamic acid type of structure. In this connection it is of great interest to note that Dubos developed the antibiotic " gramicidin " by discovering the enzyme capable of destroying a pneumococcus polysaccharide capsule, and it is of further interest to point out that the powerful new antibiotic " streptomycin " contains *N*-methyl L-glucosamine among other constituents which include an aldehydo-carbohydrate.

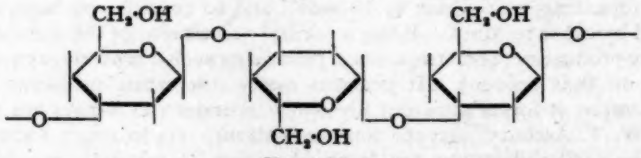
Somatic Constituents.

The somatic parts of bacterial cells have been most studied in Gram-negative organisms which are not so generally encapsulated particularly in artificial culture. In the *Salmonella* group, of which there are now 110 distinct varieties, the serological relationships are well established. The *Salmonella* may possess the motile organs mentioned previously, while from the somatic part of the cell we can isolate the so-called " O " and " Vi " antigens. In the typhoid–paratyphoid vaccines these antigens possess the immunizing power of the vaccines. Studies by Raistrick and his colleagues, Boivin, Morgan, and others (Stacey, " Advances in Carbohydrate Chemistry ", 1946, Vol. II, 162) show that these O-antigens, which are the " endotoxins " of the cell, belong to the class of carbohydrate–phospholipoid complexes. In the *Salmonella* group structural studies have not yet been carried out, but the carbohydrate components appear to be very similar to the carbohydrate residue in some proteins.

The protein constituents of the somatic part of microbial cells have not been extensively studied, but some stimulation may now come from the modern developments of food yeast on which a knowledge of the amino-acid constituents is clearly desirable.

Information is available on the structure of some other types of somatic polysaccharides, *e.g.*, yeast mannan which forms a typical copper complex, and a highly insoluble yeast " cellulose " (a so-called yeast glucan). The latter is said to possess 1 : 3-β-linkages (Figure 14).

Figure 14.



Yeast Glucan.

We have recently studied a specific somatic polysaccharide (Haworth, *loc. cit.*) from the tubercle bacillus—obtained after removal of the waxy layer by means of urea. Goebel and his colleagues have made an important discovery regarding the " C " or group specific polysaccharide from the somatic part of the pneumococcus (Goebel and Adams, *J. Exp. Med.*, 1943, 77, 435). They were able to differentiate between the " C " polysaccharide and the " F ", or heterophile, polysaccharide, inasmuch as the latter consists of the C substance combined with a fatty acid.

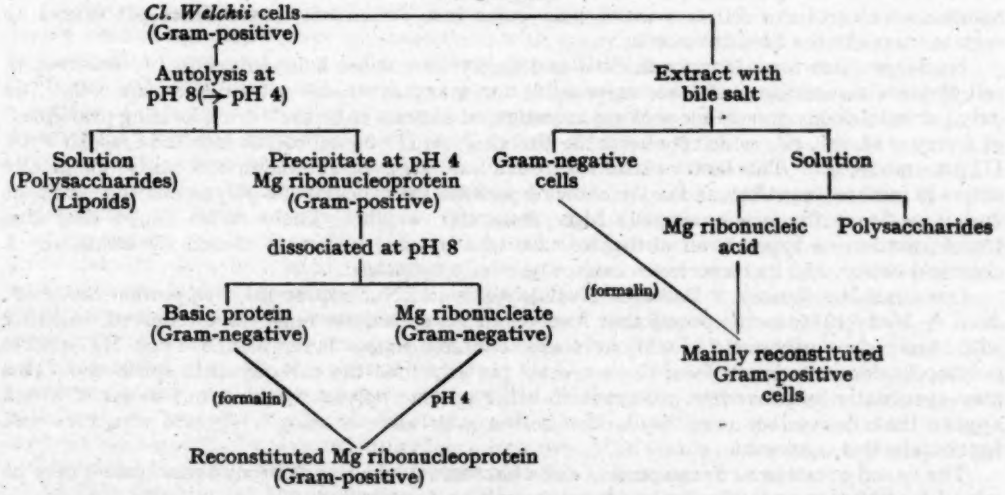
Bacterial Nucleoproteins.

Although nucleic acids were thought to be somatic constituents, the ribonucleic acid of the Gram-complex in some organisms, *e.g.*, *Cl. welchii*, is certainly located on or near the surface.

In others, *e.g.*, staphylococci, it is diffused throughout the protoplast in the form of highly packed granules.

The " Gram method " of staining micro-organisms consists in staining heat-fixed smears with an aqueous solution of a dye of the pararosaniline series, mordanting with aqueous iodine, washing with alcohol until no more of the blue dye can be extracted, then counterstaining with a red dye of the acid fuchsin series. Those cells which retain firmly the blue dye are said to be Gram-positive, while those which are decolorised by the alcohol and take up the red dye are said to be Gram-negative. Many explanations, both physical and chemical, have been advanced to account for the differential staining (Henry and Stacey, *Proc. Roy. Soc.*, 1946, *B*, 133, 391; Dubos, " The Bacterial Cell ", *loc. cit.*). It was apparent that there must be some fundamental chemical differences between Gram-positive and Gram-negative organisms to account for such diverse staining reactions. It was discovered (Henry and Stacey, 1943) that Gram-positive organisms could be made Gram-negative by various methods, *e.g.*, by enzymic attack and by chemical extraction methods. A process was developed whereby certain organisms, *e.g.*, *Cl. welchii*, could be stripped of an essential part their Gram-positive material and separated into a water-soluble Gram-negative extract and a Gram-negative cyto-skeleton. A technique was then developed whereby a constituent of the Gram-negative extract could be plated back on to the cyto-skeleton to reconstitute mainly a cell which could once more be stained Gram-positive (See Figure 15).

Figure 15.



The essential factor in the extract which could be " replated " was the magnesium salt of ribonucleic acid, and its presence at the surface of some Gram-positive organisms, and throughout the cell in others, differentiates them from some Gram-negative organisms.

The ribonucleic acids were not specific since, in the form of their magnesium salts, they could be " cross " plated back on to any receptive cell cyto-skeleton whatever their origin; for example, *Cl. welchii* magnesium ribonucleate could be plated on to yeast and *vice versa*. The Gram-complex of all microbial cells so far examined (except yeast) contained a small proportion of deoxyribonucleic acid the significance of which is not yet clear.

An interesting connection between the Gram-positive state and " smooth " and " rough " forms of colonies of organisms was demonstrated. Thus when *Streptococcus salivarius* was cultivated in a medium where the magnesium content was reduced to a minimum or where there was sufficient acid production to prevent the formation of magnesium ribonucleate, the cocci became essentially Gram-negative. Furthermore, these Gram-negative forms displayed good evidence of nucleation, and when subcultured on agar they gave rise to rough colonies whereas their normal Gram-negative relatives gave rise to colonies which were smooth. Since smoothness in a colony depends on the formation of relatively large amounts of polysaccharide it is apparent that there is a connection between the presence in the cell of the mucleic acid constituent of the Gram-positive complex and polysaccharide synthesis (cf. the work of Avery, Macleod, and McCarty, *J. Exp. Med.*, 1944, 79, 137).

The cyto-skeletons from *Cl. welchii* and from yeast gave an intense Sakaguchi reaction

indicative of the presence of basic protein material, and it was considered that the Gram-positive complex (*i.e.*, the dye-retaining material) is a high molecular complex formed by the combination of magnesium ribonucleate with a reduced basic protein substrate. A successful search was then made for this protein and for the Gram-positive complex, and it was possible to extract the complex which had the essential characteristics of a nucleoprotein. The protein constituent of this appeared to be of a novel type and was not a simple histone or a protamine.

The complex was separated from Gram-positive organisms by an autolytic procedure, using a phosphate buffer. When the nucleoprotein in neutral aqueous solution was heated at 60°, the protein constituent came down in denatured form leaving the nucleic acid in solution. This behaviour closely resembled that of Stanley's tobacco mosaic virus ribonucleoprotein. The complex could be dissociated and parts re-combined as shown in Figure 15 (Henry, Stacey, and Teece, *Nature*, 1945, **156**, 720).

The autolysis procedure in the Gram-negative group did not result in the formation of nucleoprotein. It was possible, however, to extract proteins and the two types of nucleic acid from certain Gram-negative organisms. Moreover, these could be precipitated from aqueous solution at pH 5 in the form of protein nucleates which could not be stained Gram-positive although they had a certain amount of dye-retaining character.

The next step in the work on the Gram-complex involves a study of the lytic enzymes of the cell (see Dubos, *op. cit.*). Already our colleague, Dr. H. Henry, has identified specific nucleases, carbohydrases, and proteases, all of which play a part in the autolytic breakdown of the macromolecules of the cell and which may come into action between definite pH ranges at certain stages in the life of the cells.

Nucleoproteins containing both ribo- and deoxyribo-nucleic acids are probably involved in cell-division mechanisms and are responsible for many synthetic activities of the cell. The only bacterial deoxyribonucleic acid yet investigated appears to be the " transforming principle " of Avery *et al.* (*loc. cit.*) which converts the Rough Type II pneumococcus into the Smooth Type III pneumococcus. This factor extracted from a Smooth Type III pneumococcus is biologically active in minute quantities and is somehow responsible for type specific polysaccharide synthesis and is a deoxyribonucleic acid of high molecular weight. There is no doubt that this transformation of types is an authentic case of a specific mutation caused by essentially a chemical entity, and its importance cannot be over emphasised.

One considers (Stacey, " Bacterial Nucleic Acids and Nucleoproteins, *Symposium Soc. Exp. Biol. & Med.*, 1946, in the press) that Avery and his colleagues must have removed, together with their deoxyribonucleic acid, at least a unimolecular layer of the Type III specific polysaccharide in order to form the correct " pattern " for the carbohydrate synthesis. This may eventually be proved by reference to other specific polysaccharides, but so far it would appear that deoxyribonucleic acids themselves may have a sharply specific structure and function in this connection.

The vexed question as to the presence of a bacterial nucleus and chromosome system may be solved by isolation and chemical study of the cell nucleoproteins.

It is of interest to note that certain type specific " proteins " of streptococci (" M substances ") are probably nucleoproteins, and these are located near the surface of the cells. Of great potential significance is the work of Shear and his colleagues (*J. Nat. Amer. Inst.*, 1946, **6**, 488, and previous papers) who have shown that a complex polysaccharide, related to the somatic polysaccharides of other bacteria, which can be isolated from *B. prodigiosus*, may cause extensive necrosis in transplanted tumours.

It is hoped, by continuing these studies on the structure of cell macromolecules, to gain information which will be of fundamental value regarding the physics and chemistry of all cells and of practical importance in problems of chemotherapy and immunotherapy.

OBITUARY NOTICE.

JOHN ADDYMAN GARDNER.

1867—1946.

JOHN ADDYMAN GARDNER was born on July 3rd, 1867, and passed away on May 11th, 1946. For close on fifty years he had been associated with the University of London. From 1894 to 1942 he held the appointments of Lecturer in Chemistry to St. George's Hospital Medical School and Biochemist to the Hospital, as well as other contemporary appointments for different periods.

Gardner was educated at the Grammar School, Bradford, Magdalen College, Oxford, and Heidelberg University. In his school and college days he showed great enterprise in both his work and the social activities connected with his studies. He is remembered by Old Bradfordians as excelliing on the classical side, and it was after winning an open scholarship to Magdalen that he became attracted to the study of chemistry. For some period during his undergraduate days he was President of the Oxford University Junior Scientific Club. He graduated in 1889 with First Class Honours in Chemistry in the School of Natural Science, and was awarded the Daubeny Medal.

Gardner's passion for research, which was to last unabated until his death, was developed during his undergraduate days by association with many of the eminent chemists of his day. This association was continued under Victor Meyer at Heidelberg, and secured for him a return to Oxford as Demonstrator in Chemistry. From there he published the results of researches on a variety of subjects relating to physical and organic chemistry. During this period, and for some years after his appointment to St. George's Hospital, Gardner's research work dealt largely with the chemistry of the terpenes. In collaboration with the late J. E. Marsh, Fellow of Merton, a series of communications appeared in the *Journal* (1891—97) under the title " Researches on Terpenes ", relating for the most part to the camphane group. Perhaps the most important results were obtained on the oxidation products of camphene and camphoic acid and its decarboxylated derivative, camphopyric acid (carboxyapocamphoric and apocamphoric acids respectively). The authors also described a number of halogen and phosphorus derivatives of camphor, camphene, and fenchone. Gardner continued these investigations after his appointment to St. George's Hospital, but teaching and examination work now occupied the greater part of his time. He became actively engaged upon a number of examining boards, and his sympathetic and congenial personality earned for him popularity and usefulness as Inspector of Schools throughout the country. As one of his first contributions towards biochemistry he was instrumental in improving the status of organic chemistry in the Intermediate Medical Course and Examination of the University of London.

In 1905 Gardner, at the invitation of the Director, Dr. A. D. Waller, took charge of the chemistry section of the Physiological Laboratory at that time situated in the London University side of the Imperial Institute at South Kensington, an appointment that gave him wider opportunities for research. St. George's Hospital Medical School had abandoned pre-clinical teaching, and his duties there involved chiefly the superintendence of clinical analyses and investigations. Under the new surroundings at South Kensington he and Buckmaster completed an exhaustive series of investigations on chloroform anæsthesia (*Proc. Roy. Soc.*, 1906—07). At the same time he commenced those investigations on cholesterol with which his name has been so often associated. They include a series published under the title of " The Origin and Destiny of Cholesterol in the Animal Organism " (*Proc. Roy. Soc.*, 1908—21), carried out in collaboration with a number of different workers. The earlier papers in this series were by Gardner and Dorée, and contained valuable results on the chemistry of the sterols. Coprosterol was isolated for the first time as a pure substance and was shown to be derived from the cholesterol of the body, apparently by intestinal reduction. It was converted into coprostanone and ψ-coprosterol, an epimer later to be of constitutional importance. A number of sterols related to cholesterol were also described and it was shown that hippocoprosterol and similar so-called sterols found in the fæces of herbivora were one and the same substance and a constituent of the grass on which the animals fed.

With other workers Gardner examined the cholesterol and ester content of the tissues of herbivora and omnivora fed on cholesterol-free and other diets, as a result of which it appeared that cholesterol was an essential substance strictly conserved by the animal. In later

communications—with Fox—some of the first evidence for the synthesis of cholesterol in the adult subject was forthcoming. In this series Gardner and Fraser described an accurate method for the gravimetric determination of cholesterol by utilising the insoluble compound formed by cholesterol with digitonin. They verified Windaus's observations on the accuracy attending the use of this compound in quantitative work. There is no doubt that some of the most accurate determinations of cholesterol and cholesteryl esters in human plasma were recorded by Gardner and Gainsborough in the Biochemical Laboratories at St. George's Hospital carried out during the years between the two wars and published in the *Biochemical Journal* and in the medical journals of that period. Sources of error and limits of accuracy were meticulously studied and recorded. Gardner's energy and enthusiasm, and his painstaking care and perseverance in all undertakings, attracted a continuous band of co-workers to his side and instilled into them a like appreciation for thorough and conscientious work.

Gardner's energy and enthusiasm were also applied to problems other than those associated with the sterols. His work on chloroform anæsthesia had involved him in a series of blood-gas estimations. Working with hermetically sealed gas pumps modified from existing types he recorded many accurate analyses. He was able, incidentally, to explain the traces of carbon monoxide wrongly claimed by French workers to be present in the blood of anæsthetised animals.

Always a keen angler, Gardner became interested in problems relating to river pollution, and, summarising his own extensive investigations, reported at length on " The Respiratory Exchange of Freshwater Fish " (Fishery Investigations, Vol. III, 1926). In such work the relatively large volume of water to oxygen content necessitated extreme manipulative care. It is of interest to note that with his gas pump he was able to show that trout were asphyxiated by a much smaller reduction of normal oxygen tension than were goldfish, whereas eels would thrive on a reduction to less than one-tenth of the normal oxygen tension. Gardner's insistence on accuracy in analysis may also be observed in the comprehensive account of hæmoglobin and its derivatives which he—with Buckmaster—contributed to Allen's " Commercial Organic Analysis ".

Biochemistry owes much to Gardner for the part he played in forming the Biochemical Society, and for his services as Treasurer from the time of its foundation in 1911 until a few months before his death. The new Society supplied a long-felt want to men of both chemical and medical professions who were engaged in the investigations of biochemical problems, and the membership has now risen to over a thousand.

Gardner was always keenly interested in the Chemical Society. He was a Fellow for 53 years, and was Member of Council, 1919—22. He was Reader in Physiological Chemistry, London University, and in addition to appointments already mentioned was for some years Lecturer in Organic Chemistry at the London School of Medicine for Women. He was a keen freemason, and a friend of many members of lodges in London and Yorkshire. He was a Knight of the Round Table, and for many years had been a member of the Savile Club. In 1903, he married Mrs. Henrietta White. Many of Gardner's colleagues will recall the pleasant social evenings presided over by this accomplished lady of considerable literary and linguistic attainment. She died in 1926.

During the First World War, Gardner recommended the use of the lachrymatory substance chloropicrin as a war gas, and took an active advisory part in its production on a large scale. During the Second World War, although approaching his 80th year, he was an active Air Raid Warden, going on duty in Kensington High Street during the worst raids. He was continuing some researches in the sterol field when enemy action destroyed his Kensington home. With his sister, Miss Mary Gardner, who since his wife's death had been his devoted companion, he sought available accommodation in Bradford, where an attack of bronchial pneumonia followed by heart failure ended a life of unusual accomplishment. Gardner will be remembered by his many co-workers, and indeed by nearly all the present members of the Biochemical Society, with feelings of profound gratitude for the inspiration and help afforded them individually, and for the tradition established by his example.

G. W. Ellis.

ADJOURNED ANNUAL GENERAL MEETING.

The Adjourned Hundred and Sixth Annual General Meeting was held in the Society's Rooms, Burlington House, London, W. 1, at 7.15 p.m. on Thursday, June 5th, 1947, for the purpose of receiving the accounts for the year 1946 and to appoint auditors. The President, Professor C. N. Hinshelwood, M.A., Sc.D., F.R.S., presided.

In presenting the accounts for 1946, the Treasurer drew the meeting's attention to the principal changes in the Income and Expenditure account compared with the 1945 account, and said that the increase in the cost of production of the *Journal* was accounted for largely by the considerably increased printing costs during 1946. The increase in administration costs were due to a general all round rise in the cost of administrative services of every kind and included increases in salaries, printing, stationery and postage, and House expenses, the last mentioned being due to a heavy increase in the cost of fuel and light and furniture and house decoration expenses.

The increase in the cost of the Society's contributions to the Bureau of Abstracts was exceptional since £1,200 of this sum represented a balance due to the Bureau in respect of the year 1945 which was not paid in 1945. The difference, therefore, between the total amount of £4,500 paid to the Bureau in respect of 1945 and £5,525 paid during 1946 represented an increase of £1,000, an increase due to the increased cost of production of the Abstracts for reasons similar to those given for the increased cost of the *Journal*.

On the credit side the Treasurer referred to the increased income from sales of the Society's publications which had helped to reduce the drain on the Special Reserve Fund, but pointed out that this high figure was due in a large part to the fact that a number of subscribers had been making purchases of back numbers published during the war years to complete their libraries.

In conclusion, the Treasurer referred to the necessity of drawing on the Special Reserve Fund to the extent of £4,100 to balance the accounts for 1946, and said that whilst a sufficient sum remained in the Fund to enable the Society to bear the additional cost of publishing the papers which had accumulated over the war years the Special Reserve could not also bear the additional burden of the general increase in costs with which the Society is faced. The Council was mindful of this position and had the matter under consideration.

In proposing the adoption of the accounts for 1946, Dr. F. L. Rose drew attention to the large sum which it had been found necessary to draw from the Special Reserve and said that as a member of the Publication Committee he was concerned lest the Special Reserve should be seriously depleted before the Society had had an opportunity to publish the papers awaiting publication which had accumulated during the war years and expressed the hope that the Council would give careful consideration to this problem. The proposal was seconded by Dr. J. T. Hewitt and carried. On the motion of Dr. F. R. Goss seconded by Dr. S. H. Harper, Messrs. W. B. Keen and Company were elected auditors to audit the accounts for 1947, following which the President declared the Annual Meeting terminated.

INCOME AND EXPENDITURE GENERAL PURPOSES ACCOUNT FOR THE YEAR ENDED 31ST DECEMBER, 1946.

1945 £ s. d.	1945 £ s. d.	*Income.*	1946 £ s. d.	1946 £ s. d.
	64 10 0	To Life Composition Fees (£805 16*s.* 1*d.*), one-third as Income		268 12 0
		„ Annual Subscriptions:		
		Single-body Fellows—		
1,364 5 10		Received in advance, on account of 1946	950 5 1	
4,204 1 0		Received during 1946 on account of 1946	5,143 17 0	
550 13 1		Received during 1946 on account of 1945	430 10 7	
127 15 0		Received during 1946 on account of 1944 and previous years	260 9 1	
		Joint Fellows—		
1,604 1 3		Received in advance on account of 1946	303 15 1	
5,485 4 1		Received during 1946 on account of 1946	7,507 13 4	
73 15 11		Received during 1946 on account of 1945 and previous years	100 1 4	
13,409 16 2			14,696 11 6	
		Less Payment to the Society of Chemical Industry to adjust cost of publications supplied to Joint Members	461 10 0	
13,274 6 2			14,235 1 6	
		Less Amount included in last year's Income, being valuation of Arrears as per last Balance Sheet	350 0 0	
350 0 0				
12,924 6 2			13,885 1 6	
		Add Arrears to date (£417 17*s.* 1*d.*) Estimated to realise as per Balance Sheet	350 0 0	
350 0 0				
	13,274 6 2			14,235 1 6
	472 9 0	„ Dividends on Investments		577 4 5
	481 0 5	„ Income Tax recovered		399 16 1
	25 0 0	„ Donations		— — —
	90 16 3	„ Miscellaneous Receipts...		74 5 7
	£14,408 1 10			£15,554 19 7

1945 £ s. d.	1945 £ s. d.	*Expenditure.*	1946 £ s. d.	1946 £ s. d.
		By Administration Expenses:		
4190 2 8		Office Salaries and Wages	5664 12 1	
197 7 7		Superannuation	311 18 10	
396 18 9		House Expenses, etc.	744 17 6	
84 0 0		Accountants' Charges	84 0 0	
474 10 1		Printing, Stationery and Office Expenses...	659 1 7	
217 11 3		Postages	385 10 11	
129 17 2		Miscellaneous	185 11 10	
— — —		Furniture	302 12 6	
5690 7 5			8338 5 8	
		Less Transfer to Publications and Library: £ *s.* *d.*		
538 8 9		Journal 672 8 9		
472 4 3		Abstracts A I, A II, and A III ... ... — — —		
82 3 9		Annual Reports 103 10 8		
346 13 0		Library Account 441 6 3		
			1217 5 8	
	4250 17 8			7120 19 7
		„ Expenses on Account of Conjoint Chemical Office		720 12 9
	289 1 9			
	79 14 5	„ Expenses of Meetings		253 12 0
	40 15 0	„ Donation		30 5 0
	5097 11 7	„ Balance of Expenditure on Publications to Publications Fund		4135 7 4
		„ Contribution to Library Fund:		
845 16 1		For Fittings, Furniture, Books, Periodicals, and Binding	414 5 3	
6 1 6		For Air Raid Precautions	— — —	
352 13 7		Proportion of Maintenance	366 2 9	
	1204 11 2			780 8 0
	1000 0 0	„ Transfer to Centenary Expenses Fund ...		1000 0 0
	2000 0 0	„ Transfer to Staff Pensions Fund		1000 0 0
	128 18 0	„ Expenses of Local Representatives		228 14 6
	57 18 6	„ Air Raid Precautions		— — —
	118 14 8	„ Travelling Expenses of Members of Council		200 15 3
	32 11 0	„ Loss on Exchange (Australia)		24 6 9
	107 8 1	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet		59 18 5
	£14,408 1 10			£15,554 19 7

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1946.

PUBLICATIONS FUND.

1945 £ s. d.	1945 £ s. d.	*Income.*	1946 £ s. d.	1946 £ s. d.
3753 3 6		To Publication Sales (including back numbers):		
584 19 9		Journals and Proceedings	5889 10 8	
211 2 2		Annual Reports on Progress of Chemistry	752 12 0	
		Authors' Extra Reprints	259 19 6	
13 7 3		Abstracts (Back Nos. only)	960 14 1	
9 11 2		Collective Index (do.)	23 3 1	
	4572 3 10	Other Publications	1 3 10	
				7887 3 2
1142 2 2		„ Net Proceeds of Advertisements:		
79 13 9		Journal	1024 12 1	
	1221 14 11	Annual Reports	74 11 4	
				1099 3 5
9 5 6		„ Donations:		
1500 0 0		Fellows	2 10 0	
	1509 5 6	Chemical Council	1000 0 0	
				1002 10 0
	200 0 0	„ Government Publications Grant (through the Royal Society)		750 0 0
	400 0 0	„ Allocation from the Rockefeller Grant (through the Royal Society)		— — —
	37 16 0	„ Cost of publishing Tilden Lectures: Transfer from the Tilden Lecture Fund		25 4 0
	188 4 3	„ Dividends on Investments		263 4 5
	227 16 11	„ Income Tax recovered		153 13 0
	— — —	„ Transfer from Special Reserve Fund		4100 0 0
	5097 11 7	„ Transfer from General Purposes Account (the balance of expenditure on publications)		4135 7 4
	£13,454 13 0			£19,416 5 4

1945 £ s. d.	1945 £ s. d.	*Expenditure.*	1946 £ s. d.	1946 £ s. d.
1297 1 8		By Expenses on account of Journal:		
105 12 6		Editorial Salaries	1652 10 0	
25 17 9		Superannuation	130 0 0	
4300 0 7		Editorial Postages	50 19 3	
730 6 8		Printing and Paper	6358 4 4	
476 0 3		Banding and Distribution	1300 18 10	
— — —		Authors' Reprints	476 15 1	
18 1 7		Indexing	60 0 0	
538 8 9		Miscellaneous	37 5 1	
	7491 9 9	Overhead Expenses (proportion)	672 8 9	
				10,739 1 4
	3260 13 8	„ Contributions to Bureau of Abstracts:		
		Balance for 1945	1235 18 8	
		Grants, 1946	5525 0 0	
				6760 18 8
	— — —	„ Distribution of Abstracts		52 10 5
	1450 0 0	„ Transfer to Special Reserve Fund (Quinquennial Index)		300 0 0
	1252 9 7	„ Annual Reports on the Progress of Chemistry: Printing, Honoraria, and Overhead Expenses		1563 14 11
	£13,454 13 0			£19,416 5 4

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1946.

LIBRARY.

1945			*Income.*	1946					
£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.
			To Contribution for Fittings, Furniture, Books, Periodicals and Binding:						
845	16	1	Transfer from General Purposes Account ...	414	5	3			
65	10	0	Transfer from Special Reserve Fund (deferred expenditure)	112	17	6			
			Air Raid Precautions:						
6	1	6	Transfer from General Purposes Account ...	—	—	—			
		917	7	7				527	2	9
			„ Contributions towards maintenance:						
			Through the Chemical Council:						
			Chemical Society (transfer from General Purposes Account)	366	2	9			
352	13	7	Royal Institute of Chemistry	701	15	6			
734	15	0	Society of Chemical Industry	381	7	10			
382	1	5	Faraday Society	76	5	6			
—	—	—	From the Chemical Council	900	8	6			
337	12	3							
		1807	2	3				2426	0	1
			„ Contributions, etc., received from other sources towards maintenance:						
			Association of British Chemical Manufacturers	100	0	0			
100	0	0	Biochemical Society	21	0	0			
21	0	0	British Association of Chemists	50	0	0			
50	0	0	Faraday Society	—	—	—			
26	5	0	Institute of Brewing	50	0	0			
50	0	0	Society of Dyers and Colourists	10	10	0			
10	10	0	Society of Public Analysts and other Analytical Chemists	21	0	0			
21	0	0	Fellows	—	—	—			
	16	6	Miscellaneous receipts	54	2	0			
55	8	1							
		334	16	7				306	12	0
		£3059	6	5				£3259	14	10

1945			*Expenditure.*	1946					
£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.
			By Capital and Extraordinary Expenditure						
358	11	6	Books and Periodicals *	300	17	4			
23	5	3	Binding	17	10	0			
—	—	—	Furniture	8	15	5			
229	9	4	Steel Shelving	—	—	—			
300	0	0	Transfer to Special Reserve Fund	—	—	—			
6	1	6	Air Raid Precautions	—	—	—			
		917	7	7				527	2	9
			„ Maintenance:						
1611	12	10	Salaries	2018	11	10			
124	11	5	Superannuation of Library Staff	146	11	0			
39	18	0	Postages	45	8	5			
19	3	7	Miscellaneous Expenses	80	14	7			
346	13	0	Overhead Expenses (proportion)	441	6	3			
		2141	18	10				2732	12	1
		£3059	6	5				£3259	14	10

* Other than those received in exchange.

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1946.

SPECIAL RESERVE FUND.

1945			*Income.*	1946			1945			*Expenditure.*	1946		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
223	7	0	To Dividends on Investments	340	13	9							
36	11	10	„ Interest on Deposit	34	12	1							
123	7	7	„ Income Tax recovered	140	4	10							
							383	6	5	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	515	10	8
£383	6	5		£515	10	8	£383	6	5		£515	10	8

RESEARCH FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
357	11	3	To Dividends on Investments	379	4	5	308	0	0	By Grants	526	9	10
380	2	4	„ Income Tax recovered	323	17	10	20	0	0	„ Honoraria: Longstaff Medallist	—	—	—
15	12	0	„ Repayment of Grants	30	15	3	21	0	0	Hugo Müller Lecturer	—	—	—
2	9	6	„ Interest on Deposit	3	5	6	3	5	0	„ Longstaff Medal	—	—	—
—	—	—	„ Donations	20	0	0	2	12	6	„ Miscellaneous Expenses	9	19	8
—	—	—	„ Sale of Apparatus	15	4	11				„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	236	17	0
—	—	—	„ Grants not applied for		18	7	400	17	7				
£756	15	1		£773	6	6	£755	15	1		£773	6	6

SPECIAL PUBLICATIONS FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.	£	s.	d.
						To Sales of Publications:									
11	8	6				Memorial Lecture, Vol. I	10	15	2						
10	10	3				„ „ Vol. II	9	3	6						
6	18	1				„ „ Vol. III	5	13	10						
10	8	8				Faraday Lectures	3	13	10						
3	13	10				Portraits	2	8	0						
1	4	3				Other publications	5	9	5						
			44	3	7					37	2	9			
			74	0	8	„ Dividend on Investment				74	0	8			
			24	16	11	„ Interest on Deposit				26	0	11			
			£143	1	2					£137	4	4	£143	1	2

£	s.	d.		£	s.	d.
143	1	2	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	137	4	4
£143	1	2		£137	4	4

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1946.

CENTENARY EXPENSES FUND.

1945	*Income.*	1946	1945	*Expenditure.*	1946
£ s. d.		£ s. d.	£ s. d.		£ s. d.
1000 0 0	To Contribution from General Purposes Account	1000 0 0	— — —	By Miscellaneous Expenses	654 18 10
27 10 4	„ Interest on Deposit	32 19 6	1027 10 4	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	378 0 8
£1027 10 4		£1032 19 6	£1027 10 4		£1032 19 6

STAFF PENSIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
2000 0 0	To Transfer from General Purposes Account	1000 0 0	396 5 0	By Pensions paid during 1946	840 0 0
69 7 10	„ Dividends on Investments	100 11 5		„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	306 14 10
40 18 3	„ Income Tax recovered	34 1 3	1719 14 11		
5 13 10	„ Interest on Deposit	12 2 2			
£2115 19 11		£1146 14 10	£2115 19 11		£1146 14 10

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
27 5 2	To Dividends on Investments	28 10 3	150 0 0	By Harrison Prize	— — —
25 2 0	„ Income Tax recovered	25 2 0	14 14 0	„ Harrison Plaque	— — —
2 11	„ Interest on Deposit	— — —		„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	53 12 3
112 3 11	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	— — —	— — —		
£164 14 0		53 12 3	£164 14 0		53 12 3

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1946.

SPECIAL LECTURES FUND.

1945	*Income.*	1946	1945	*Expenditure.*	1946
£ s. d.		£ s. d.	£ s. d.		£ s. d.
33 18 4	To Dividends on Investments	34 9 11	25 0 0	By Honoraria	50 0 0
11 11 2	„ Income Tax recovered	11 11 2	5 2 6	„ Lecture Expenses	3 17 5
13 5	„ Interest on Deposit	13 5		„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet	— — —
— — —	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	7 2 11	16 0 5		
£46 2 11		£53 17 5	£46 2 11		£53 17 5

THE FARADAY LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
6 11 2	To Dividends on Investments	6 17 10	13 7 5	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	13 14 1
6 11 3	„ Income Tax recovered	6 11 3			
5 0	„ Interest on Deposit	5 0			
£13 7 5		£13 14 1	£13 7 5		£13 14 1

THE TILDEN LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
43 2 6	To Dividends on Investments	44 16 5	15 15 0	By Honoraria	47 5 0
30 11 0	„ Income Tax recovered	30 11 0	23 11 1	„ Lecture Expenses	14 10 11
3 8	„ Interest on Deposit	3 0	37 16 0	„ Transfer to Publications Fund, for cost of publication of Lectures	25 4 0
3 4 11	„ Balance, being Excess of Expenditure over Income, carried to Balance Sheet	11 9 6			
£77 2 1		£86 19 11	£77 2 1		£86 19 11

THE CHEMICAL SOCIETY.—BALANCE SHEETS, 31st December, 1946.

GENERAL PURPOSES.

1945			*Liabilities.*	1946		
£ s. d.	£ s. d.			£ s. d.	£ s. d.	
	1,262 6 8		To Subscriptions received in advance ...		5,684 19 11	
	7,768 9 10		„ Sundry Creditors (Printing and other Expenses and Publications in advance)		6,831 13 8	
	950 0 0		„ Amount due to Special Reserve Fund ...		— — —	
	1,000 0 0		„ Amount due to Staff Pensions Fund ...		— — —	
			„ Excess of Assets over Liabilities as per last Balance Sheet	22,064 3 5		
21,827 15 4						
129 0 0			*Add* Life Composition Fees (805 16*s.* 1*d.*) (two-thirds)	537 4 1		
— — —			*Add* Profit on realisation of investment	56 19 0		
			Add Excess of Income over Expenditure for year	59 18 5		
107 8 1						
	22,064 3 5				22,718 4 11	
	£33,044 19 11				£35,234 18 6	

1945		*Assets.*	1946	
£ s. d.			£ s. d.	
25,161 13 0		By Investments as per Schedule cost or value when acquired		25,368 12 0
6,376 14 8		„ Sundry Debtors		5,806 16 2
350 0 0		„ Subscriptions in Arrear (£417 17*s.* 1*d.*). Estimated to realise ...		350 0 0
127 8 0		„ Stock of Paper (Journal, Annual Reports and Quarterly Reviews) ...		727 16 4
1,029 4 3		„ Cash at Bank and in hand		2,981 14 0
£33,044 19 11				£35,234 18 6

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1946.

PUBLICATIONS FUND.

1945	*Liabilities.*	1946	1945	*Assets.*	1946
£ s. d.		£ s. d.	£ s. d.		£ s. d.
9537 8 8	To Excess of Assets over Liabilities as per last Balance Sheet	9537 8 8	9537 8 8	By Investments as per Schedule (cost or value when acquired)	9537 8 8
£9537 8 8		£9537 8 8	£9537 8 8		£9537 8 8

SPECIAL RESERVE FUND.

£ s. d.	£ s. d.	*Liabilities.*	£ s. d.	£ s. d.	£ s. d.	*Assets.*	£ s. d.	£ s. d.
	65 10 0	To Sundry Creditors			16,200 0 0	By Investments as per Schedule (cost or value when acquired)		16,162 10 2
		Reserve for Publications (including Quinquennial Index) as per last			950 0 0	„ Sundry Debtor (General Purposes Account)		300 0 0
12,410 0 7		Balance Sheet	13,685 0 7		2,642 4 7	„ Cash at Bank (including Deposit) and on Deposit in Post Office Savings Bank and London Savings Bank		1542 5 3
1450 0 0		*Add* Amount transferred from General Purposes Account	300 0 0					
13,860 0 7			13,985 0 7					
175 0 0		*Less* Amount transferred to Bureau of Abstracts	— — —					
— — —		*Less* Amount transferred to General Purposes Account	4100 0 0					
	13,685 0 7			9885 0 7				
		„ Reserve for Library Books and Binding						
1400 1 6		as per last Balance Sheet	1634 11 6					
300 0 0		*Add* Amount transferred from General Purposes Account...	— — —					
1700 1 6			1634 11 6					
65 10 0		*Less* Amount transferred to General Purposes Account for Library Books	112 17 6					
	1634 11 6			1521 14 0				
	3350 0 0	„ Reserve for Research Fund as per last Balance Sheet		3350 0 0				
	100 0 0	„ Emile Mond Bequest as per last Balance Sheet		100 0 0				
		„ Excess of Income over Expenditure						
573 16 1		brought forward	957 2 6					
383 6 5		*Add* Excess of Income over Expenditure for year	515 10 8					
957 2 6			1472 13 2					
— — —		*Deduct* Loss on realisation of Investment	37 9 10					
	957 2 6			1435 3 4				
	£19,792 4 7			£18,004 15 5	£19,792 4 7			£18,004 15 5

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1946.

RESEARCH FUND.

1945 £ s. d.	1945 £ s. d.	*Liabilities.*	1946 £ s. d.	1946 £ s. d.
	144 14 0	To Sundry Creditors		355 2 4
18,978 19 10		„ Excess of Assets over Liabilities as per last Balance Sheet	19,379 17 5	
400 17 7		*Add* Excess of Income over Expenditure for year	236 17 0	
19,379 17 5			19,616 14 5	
— — —		*Add* Received from Sir Martin Forster—Legacy	500 0 0	
	19,379 17 5			20,116 14 5
	£19,524 11 5			£20,471 16 9

1945 £ s. d.	*Assets.*	1946 £ s. d.
18,608 15 7	By Investments as per Schedule (cost or value when acquired)	19,108 15 7
915 15 10	„ Cash at Bank (including Deposit) and on deposit in Post Office Savings Bank	1,363 1 2
		£20,471 16 9

SPECIAL PUBLICATIONS FUND.

1945 £ s. d.	1945 £ s. d.	*Liabilities.*	1946 £ s. d.	1946 £ s. d.
	13 0	To Sundry Creditors		9 7
2704 10 8		„ Excess of Assets over Liabilities as per last Balance Sheet	2847 11 10	
143 1 2		*Add* Excess of Income over Expenditure for year	137 4 4	
	2847 11 10			2984 16 2
	£2848 4 10			£2985 5 9

1945 £ s. d.	*Assets.*	1946 £ s. d.
1 2 2	By Sundry Debtors	3 1 0
1600 0 0	„ Investment as per Schedule (cost or value when acquired)	1600 0 0
1247 2 8	„ Cash at Bank (including Deposit) and on deposit in the Post Office Savings Bank and London Savings Bank	1382 4 9
		£2985 5 9

CENTENARY EXPENSES FUND.

1945			*Liabilities.*	1946			1945			*Assets.*	1946		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			To Sundry Creditors			654 18 10				By Cash at Bank (including Deposit) and on deposit in Post Office Savings Bank and London Savings Bank	3165	4	6
1104	14	8	„ Excess of Assets over Liabilities as per last Balance Sheet	2132	5	0							
1027	10	4	*Add* Excess of Income over Expenditure for year	378	0	8							
		2132	5	0		2510	5	8					
		£2132	5	0		£3165	4	6	£2132	5	0		£3165	4	6

STAFF PENSIONS FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			396	5	0	To Sundry Creditors				1000	0	0	By Sundry Debtor (General Purposes Account)			
4511	8	0				„ Excess of Assets over Liabilities as per last Balance Sheet	6231	2	11	4619	10	10	„ Investments as per Schedule (cost or value when acquired)	4619	10	10
1719	14	11				*Add* Excess of Income over Expenditure for year	306	14	10	1007	17	1	„ Cash at Bank (including Deposit) and on deposit in the Post Office Savings Bank	1918	6	11
		6231	2	11					6537	17	9					
		£6627	7	11			£6537	17	9	£6627	7	11		£6537	17	9

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
						To Excess of Assets over Liabilities as per last Balance Sheet	1146	6	11	1101	7	11	By Investments as per Schedule (cost or value when acquired)	1101	7	11
1256	10	10				*Add* Excess of Income over Expenditure for year	53	12	3	44	19	0	„ Cash at Bank	98	11	3
							1199	19	2							
1256	10	10				*Deduct* Excess of Expenditure over Income for year										
113	8	11							1199	19	2					
		1146	6	11												
		£1146	6	11			£1199	19	2	£1146	6	11		£1199	19	2

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1946.

SPECIAL LECTURES FUND.

1945 £ s. d.		1945 £	*Liabilities.*	1946 £ s. d.	1946 £	1945 £ s. d.		1946 £ s. d.
			To Sundry Creditor		25 0 0	1000 0 0	By Investment as per Schedule (cost or value when acquired	1000 0 0
1208 4 1	„ Excess of Assets over Liabilities as per last Balance Sheet			1224 4 6		224 4 6	„ Cash at Bank	242 1 7
16 0 5	*Add* Excess of Income over Expenditure for year							
	Deduct Excess of Expenditure over Income for year			7 2 11				
		1224 4 6			1217 1 7			
		£1224 4 6			£1242 1 7	£1224 4 6		£1242 1 7

THE FARADAY LECTURE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
445 2 3		To Excess of Assets over Liabilities as per last Balance Sheet ...	458 9 8	369 4 0	By Investment as per Schedule (cost or value when acquired)	369 4 0
13 7 5		*Add* Excess of Income over Expenditure for year	13 14 1	89 5 8	„ Cash at Bank	102 19 9
	458 9 8					
	£458 9 8		£472 3 9	£458 9 8		£472 3 9

THE TILDEN LECTURE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
1970 16 0		To Excess of Assets over Liabilities as per last Balance Sheet	1967 11 1	1878 14 10	By Investments as per Schedule (cost or value when acquired)	1878 14 10
3 4 11		*Deduct* Excess of Expenditure over Income for year ...	11 9 6	88 16 3	„ Cash at Bank	77 6 9
	1967 11 1					
	£1967 11 1		£1956 1 7	£1967 11 1		£1956 1 7

SCHEDULE OF INVESTMENTS.

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December 1946.*
	£ s. d.	£ s. d.
£11,426 15s. 0d. 3½% Conversion Stock, 1961, or after	8874 2 2	13,140 15 3
£600 4% Funding Stock, 1960/90	480 0 0	727 10 0
£408 2s. 6d. 3% Funding Stock, 1959/69	394 11 5	443 16 9
£100 3% Savings Bonds, 1955/65	100 0 0	108 10 0
£175 3% Savings Bonds, 1965/75	175 0 0	193 16 3
£1200 14s. 9d. 3% Savings Bonds, 1960/70	1200 14 9	1311 16 2
£150 2½% Savings Bonds, 1964/67	150 0 0	157 7 6
£1200 2½% Defence Bonds	1200 0 0	1200 0 0
£3825 1s. 6d. Local Loans, 3%	3629 6 9	3825 1 6
£1520 14s. 3d. Cardiff Corporation 3% Stock, 1914/54	1650 0 0	1528 6 3
£2400 Bristol Corporation 2½% Debenture Stock, 1957	2070 2 0	2424 0 0
£787 London, Midland and Scottish Railway 4% Debenture Stock	839 3 7	908 19 8
£3713 London, Midland and Scottish Railway 4% Preference Stock	3572 0 4	2265 7 1
£1200 London and North Eastern Railway 5% Debenture Stock ...	1033 11 0	1200 0 0
	£25,368 12 0	£29,435 6 5

PUBLICATIONS FUND.

£5260 19s. 9d. 3½% Conversion Stock, 1961, or after	3645 12 8	6050 2 9
£1000 3% Savings Bonds, 1955/65	1000 0 0	1085 0 0
£1261 1s. 11d. 3% Savings Bonds, 1960/70	1261 1 11	1377 15 0
£3344 3s. 4d. Local Loans 3%	3175 1 6	3344 3 4
£603 London, Midland and Scottish Railway 4% Guaranteed Stock	457 12 7	636 3 4
	£9537 8 8	£12,493 4 5

RESEARCH FUND.

£10,177 16s. 1d. 3½% Conversion Stock, 1961, or after	8833 2 3	11,704 9 5
£500 Defence Bonds, 4th Issue	500 0 0	500 0 0
J4741 4s. 10d. Local Loans, 3%	4498 11 0	4741 4 10
£806 Victoria 3% Stock, 1929/49	706 6 2	822 2 5
£1000 London and North Eastern Railway 4% 2nd Guaranteed Stock	1010 0 0	985 0 0
£1034 Great Western Railway 2½% Debentures	1049 15 11	956 9 0
£1483 London, Midland and Scottish Railway 4% Debenture Stock	1508 3 6	1712 17 4
£1122 Metropolitan Water Board 3% "B" Stock	1002 16 9	1144 8 10
	£19,108 15 7	£22,566 11 10

SPECIAL RESERVE FUND.

£1000 3% Defence Bonds	1000 0 0	1000 0 0
£2400 2½% National War Bonds, 1949/51	2400 0 0	2469 0 0
£3700 2½% National War Bonds, 1952/54	3700 0 0	3871 2 6
£1500 3% Savings Bonds, 1955/65	1500 0 0	1627 10 0
£7476 1s. 9d. 2½% Savings Bonds, 1964/67	7562 10 2	7793 16 6
	£16,162 10 2	£16,761 9 0

SPECIAL PUBLICATIONS FUND.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December, 1946.*
	£ s. d.	£ s. d.
£2115 8s. 10d. 3½% Conversion Stock, 1961, or after	£1600 0 0	£2432 15 1

STAFF PENSIONS FUND.

£683 6s. 1d. 3½% Conversion Stock, 1961, or after	527 13 9	785 15 11
£150 2½% National War Bonds, 1951/53	150 0 0	156 15 0
£170 3% Savings Bonds, 1955/65	170 0 0	184 9 0
£300 3% Savings Bonds, 1960/70	300 0 0	327 15 0
£1000 3% Savings Bonds, 1965/75	1000 0 0	1107 10 0
£2100 2½% Savings Bonds, 1964/67	2100 0 0	2189 5 0
£391 17s. 4d. Local Loans, 3%	371 17 1	391 17 4
	£4619 10 10	£5143 7 3

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£61 15s. 8d. 3½% Conversion Stock, 1961, or after	50 1 5	71 0 11
£1255 London, Midland and Scottish Railway 4% Debenture Stock	1051 6 6	1449 10 6
	£1101 7 11	£1520 11 5

SPECIAL LECTURES FUND.

£1299 9s. 4d. 3½% Conversion Stock, 1961, or after	£1000 0 0	£1494 7 9

THE FARADAY LECTURE FUND.

£374 19s. 0d. 3½% Conversion Stock, 1961, or after	£369 4 0	£431 3 10

THE TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Stock, 1959/69	386 12 10	455 18 6
186 National Provincial Bank Shares £5 each, £1 paid "B"	678 18 0	846 6 0
£532 London Transport "B" 5% Stock	625 2 0	662 6 10
£220 Metropolitan Water Board (Kent Water Works) 3% Deb. Stock	188 2 0	221 2 0
	£1878 14 10	£2185 13 4

F. P. DUNN, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and the Investments.

W. B. KEEN & CO.,
Chartered Accountants.

FINSBURY CIRCUS HOUSE,
BLOMFIELD STREET, E.C.2.
19*th May*, 1947.

MADE TO LAST LONGER

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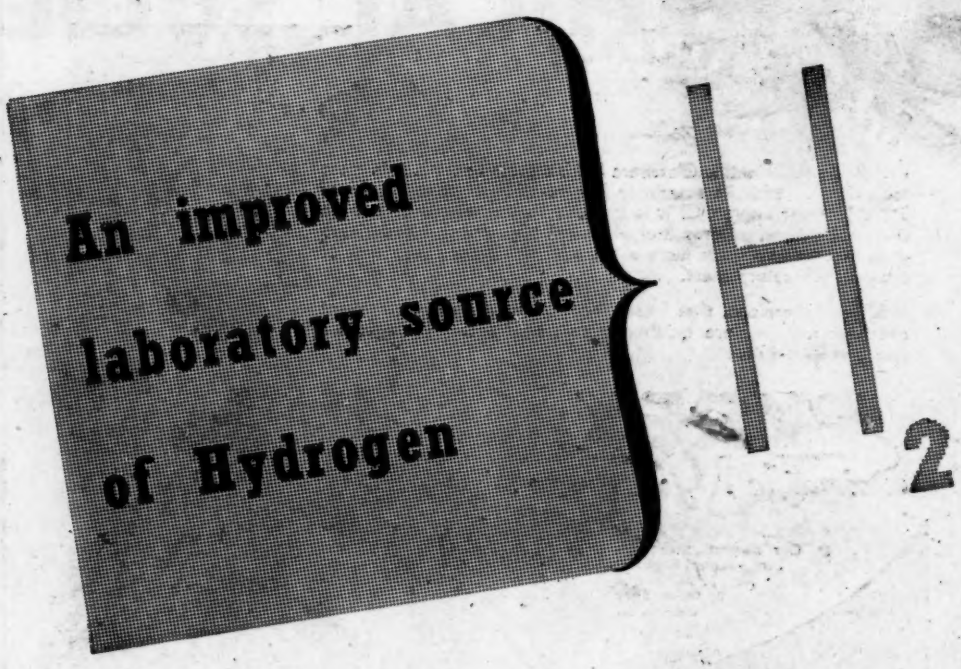

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Five of the pellets (each weighing 0.1g.) in dilute sodium chloride solution at room temperature yield about 200 c.c. of hydrogen in five minutes.

The pellets are prepared from a formula developed for Admiralty purposes during the war and are already finding many convenient applications in the laboratory.

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